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Johnny Mahlangu; S Diop; Michelle Lavin

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Diagnosis and treatment challenges in lower resource countries: State-of-the-art

Johnny Mahlangu[1,2] | **Saliou Diop**[3] | **Michelle Lavin**[4,5]

[1]Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, the National Health Laboratory Service, Johannesburg, South Africa

[2]Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa

[3]Department of Hematology, University Cheikh Anta Diop, Dakar, Senegal

[4]National Coagulation Centre, St. James's Hospital, Dublin, Ireland

[5]Irish Centre for Vascular Biology, School of Pharmacy & Biomolecular Sciences, RCSI, Dublin, Ireland

Correspondence
Johnny Mahlangu, Room 50, Area 454, Charlotte Maxeke Johannesburg Academic Hospital, 7 York Road, Parktown, Johannesburg, South Africa.
Email: johnny.mahlangu@nhls.ac.za

Abstract

The 2022 World Federation of Haemophilia Annual Global Survey (AGS) reports that 454,690 patients with inherited bleeding disorders (IBD) have been identified globally. While this represents noteworthy progress, haemophilia epidemiology data indicate that 75% of people with inherited bleeding disorders living in low-income and low-to-middle-income countries have yet to be diagnosed. The AGS also revealed that 11 billion clotting factor units are available to treat haemophilia A and B globally. Due to a lack of finance, these treatments are unavailable to haemophilia in low-income countries with a consequence lack of access equity for haemophilia treatment in these communities. This sobering reality is not limited to haemophilia but applies to von Willebrand Disease (VWD). While VWD is the most prevalent IBD, only 103,844 people living with this condition have been diagnosed globally. Of the diagnosed patients, only a fraction live in low- or middle-income countries. Moreover, the majority of VWD patients are still treated sub-optimally without replacement therapies or prophylaxis, both of which are now accepted as global standards of care. In this state-of-the-art review, the authors reflect on three issues. First, the minimum elements required to diagnose haemophilia in a resource-constrained setting are identified. Second, this review points to the critical stakeholders and outlines their roles in removing access to haemophilia treatment barriers. Finally, the authors examine von Willebrand disease's ongoing diagnostic and treatment challenges and compare these to haemophilia. With the rapidly evolving novel therapies, the therapeutic landscape of all IBD will likely change for the better.

KEYWORDS
diagnosis, haemophilia, low resource, treatment, von Willebrand disease

1 | INTRODUCTION

In the last several decades, the bleeding disorders community has seen an unprecedented evolution of novel therapies for treating inherited disorders. These therapies have included recombinant clotting factor concentrated (rCFC) and CFC with improved pharmacokinetics and non-factor therapies.[1] More recently, with the approval of haemophilia A and B AAV-mediated gene transfer, we have ushered in a new era of gene therapy for haemophilia A and B.[2,3] Despite these remarkable advances, most people living with inherited bleeding disorders (PwIBD)

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have limited or no access to both diagnosis and treatment resources and expertise.[4] The Institute of Medicine defines access to optimal health care as the timely use of personal health services to achieve the best health outcomes.[5] To achieve the best health outcomes, it is sensible to start with making a diagnosis, identifying appropriate treatment options and removing all barriers to both. We recognise that in resource-constrained settings, the challenge of facilitating access to diagnosis and treatment of inherited bleeding disorders is insurmountable. In this review, we aim to highlight the essential minimum elements to make a diagnosis, the critical stakeholders and their roles in identifying and removing barriers to treatment access for haemophilia. Lastly, we will discuss the ongoing diagnostic and treatment challenges of von Willebrand disease, compare these to haemophilia and suggest possible solutions.

2 | ACCESS TO DIAGNOSIS FOR BLEEDING DISORDERS: WHAT ARE THE MINIMAL REQUIREMENTS TO DETERMINE THE CORRECT TREATMENT?

The most recent World Federation of Haemophilia (WFH) data indicate that the diagnosis of people with inherited bleeding disorders (PwIBD) in low-income countries (LIC) and low to middle-income countries (LMIC) is low, with only 6.3% of those diagnosed in these countries which contribute 59% of the global population.[6,7] This contrasts with the 55% of PwIBD diagnosed in high-income countries (HIC), contributing to 18% of the world's population.

Analysis of the current World Bleeding Disorders Registry (WBDR) shows that the current median age at diagnosis of PwIBD in LIC is late when compared to upper middle-income countries (UMIC) and HIC, which are three and four decades earlier, respectively.[8] These various gaps reflect the many challenges that result in early mortality of patients before confirmation of their diagnosis, lack of awareness among the population and health care professionals, low numbers of identified patients that prevent them from being considered in health policies, absence of adequate care as starting prophylaxis early, before 3 years as recommended by WFH guidelines. It is, therefore, essential to define minimal requirements to improve diagnosis and allow correct treatment in the LICs and LMICs. These minimum requirements include adequate healthcare system organisation, community awareness and trained healthcare providers (HCP), and availability of good-quality coagulation laboratories.

2.1 | Adequate organisation of the healthcare system

According to the World Health Organization (WHO),[9] universal health coverage means that all people have access to the full range of quality health services they need, when and where they need them, without financial hardship. Applying this vision to diagnosing bleeding disorders means that the system must enable these diseases to be suspected from the community level in rural areas and organise a referral system to ensure rapid confirmation in a better-equipped laboratory.

Most LICs have a pyramid-type health care system, with basic health care provided from the community level, where there's no HCP, to the referral level in hospitals in major cities. Bleeding disorders should be integrated into this health system model with a clear definition of the activity packages required for each level, as shown in Figure 1. To be set up by the health authorities, this organisation requires that a suitable matrix already exists, initiated by specialised doctors and patient groups, with the support of international organisations.[10] In Africa, the question of geographical and financial accessibility to care is crucial, as direct payment can act as a significant brake, encouraging patients to continue using traditional practitioners who may not have the tools to diagnose the disease. Describing the patient journey would enable understanding the reasons for the delay of diagnosis linked to the organisation of the healthcare system to choose the solution with the most significant impact.

2.2 | Community awareness and trained healthcare providers

The second minimum requirement is the availability of a community aware of bleeding disorders and of HCPs trained in diagnosis with good expertise in haemostasis. Poverty is often associated with a lack of access to information and, therefore, with the spread of false beliefs.[11] Deconstructing this fact in the community requires effective awareness-raising by patient groups and local leaders, including traditional practitioners who are often the first to see patients. Using digital health systems has demonstrated a vast potential to improve education and self-management for PWH.[12] Organised outreach campaigns are thus opportunities not only to identify new patients but also to educate the population. Similarly, the availability of expertise in haemostasis must be ensured through basic training and a continuing education program that should not only be limited to the big cities but rather be provided in remote areas so that screening can be carried out at this level.[13]

2.3 | Availability of good-quality coagulation laboratory facilities

Laboratories need to be organised as a network from the peripheral health centres to the reference centres in major hospitals. At least screening tests such as PT and APTT should be performed in these peripheral centres, which generally have a haemostasis laboratory for the pre-anaesthesia work-up for emergency obstetric care. There must be at least one reference centre where the following tests are carried out: coagulation factor assays, screening and titration of inhibitors, diagnosis of Willebrand's disease and possibly diagnosis of constitutional thrombopathies. Plasma transfer is sometimes problematic, and it is crucial to define procedures to facilitate the reference-counter-reference system. Essential elements for these

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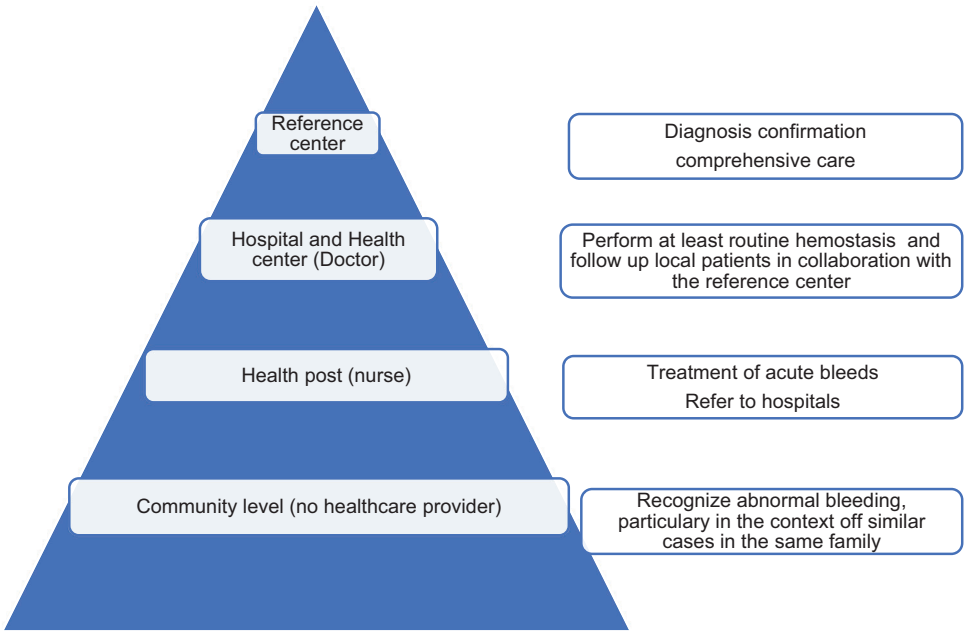


FIGURE 1 Algorithm for organizing care according to the heath pyramid.

laboratories include a network of biologists with variable expertise in haemostasis; well-maintained equipment (refrigerators, pipettes, water baths, coagulometers, centrifuges); reagent supply circuits ensuring reasonable regularity. From a technical point of view, it is essential to consider the quality of blood sampling, the conditions under which samples are transported between laboratories, and the traceability of documents. The assurance of appropriate technical skills is required for at least the following tests: Prothrombin time, activated Partial Thromboplastin Time, mixing studies and factor VIII and IX measurements.[14] The Second step will be the Bethesda test, Von Willebrand factor activity and Platelet function tests. Quality controls are essential and should be organised inside the country, and participation in external programs such as the WFH International External Quality Assurance Scheme (IEQAS) is also required.[15] Genetic testing is optional as a minimal requirement, but collaboration in the research program should be an opportunity to send samples to more specialised laboratories.

2.4 | Potential of point-of-care to facilitate access to diagnosis

While haemophilia musculoskeletal assessment point-of-care (POC) ultrasound is now available and used in many parts of the world, including LMIC/LICs, the POC laboratory diagnosis for haemophilia and VWD is lagging. Many currently available POC coagulometers can measure the international normalised ratio but not the activated prothrombin time, clotting factor levels or VWF. When instruments capable of these measurements are standardised, validated and accredited in the future, they will significantly improve the diagnosis of haemophilia and VWD.

3 | BETTER ACCESS TO HAEMOPHILIA THERAPIES: WHAT CAN STAKEHOLDERS DO?

The widely used treatment approaches for haemophilia care include clotting factor replacement therapies, administered episodically to treat acute bleeding events or prophylactically to prevent bleeding.[4] The current guidelines recommend, and clinical practice protocols have implemented prophylaxis as the global standard of care in haemophilia management. The treatment agents available for prevention are diverse and include plasma-derived and recombinant half-life clotting factor concentrates, extended half-life clotting factor concentrates and non-factor therapies.[16] The recently approved haemophilia A and B gene therapies may be considered as part of long-term prophylaxis in haemophilia patients.[2,3] These therapies are administered intravenously or subcutaneously at various dose regimens to the individual patient's treatment goals.

The currently available haemophilia treatment armamentarium will change the inequitable treatment access in haemophilia in which 75% of PWH living in LIC and LMICs have limited or no access to essential haemophilia treatment. While the total clotting factor volume available globally has increased to over 11 billion units of FVIII and FIX, only 19% of these clotting factors are available to PWH living in LIC and LMIC, who constitute 71% of the global population.[7] The critical limitation of replacement therapy supply in low-income countries is limited plasma for plasma-derived products and the absence of manufacturing facilities for recombinant products. The recent addition of non-factor therapies to the therapeutic toolbox is expected to improve treatment access for haemophilia patients. The critical determinants of improved haemophilia treatment access include the availability of treatments, acceptability of treatments and treatment affordability facilitated by various key stakeholders.

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3.1 | The role of the stakeholders to improve treatment access

Diverse stakeholders are critical in facilitating treatment access, removing access barriers and monitoring treatment impact. The essential stakeholders include people with haemophilia (PWH) and their organisations, health care providers (HCP) and health delivery facilities and both public (government) and private (health insurance) funders of treatment. Each of these stakeholders is accountable for critical, unique, and complimentary roles in removing barriers to access, ensuring treatment availability, assuring treatment acceptability and reducing treatment costs (affordability). The functions of stakeholders in addressing the availability, acceptability and affordability of treatment are summarised in Table 1. While many of these roles may overlap, there are unique accountabilities to be highlighted.

The role of patients in removing treatment access barriers should be acknowledged and addressed. Experience with many other chronic diseases, such as HIV and tuberculosis treatment, has demonstrated that direct patient involvement in access efforts does yield the desired results,[6] leading to treatment availability, acceptability and affordability. In advocating for these access elements, patients must develop disease literacy and expertise to confront dismissive arguments from other stakeholders. Literacy should not be an issue in haemophilia as patients are organised under the auspices of the World Federation of Haemophilia, which supports and provides the required advocacy resources and training.[17]

Healthcare providers and facilities play a unique role in ensuring the availability and acceptability of treatment to be accessed. Evaluating the risk-benefit profile of each therapeutic product requires the expertise and knowledge of HCPs, which is usually acquired through participation in clinical trials or post-trial real-world experience. The HCPs must contextualise the treatment in terms of the goals and outcomes of therapy and educate both the patients and funders on the benefits of the old and new therapies.

In ensuring accessibility, affordability and availability, the role of healthcare providers in developing a comprehensive portfolio of treatments should be emphasised (Table 1). This includes the initial use of low-dose prophylaxis to embed the practice of prophylaxis in clinical practice and lower the cost to be acceptable to funders. Indeed, data from LIC/LMIC indicate that low-dose prophylaxis is better than episodic treatment.[18–20] Low-dose prophylaxis is now included in current international haemophilia treatment guidelines.[4]

TABLE 1 Some roles of stakeholders in facilitating treatment access in haemophilia.

	Availability of treatment	Acceptability of treatment	Affordability of treatment
Person with haemophilia/Patient organization	1. Develop critical mass activists to advocate for treatment access. 2. Recruit participants in clinical studies to broaden access. 3. Collaboration with other stakeholders 4. Develop treatment literacy early to support patient involvement	1. Develop expertise in the science of therapies. 2. Participate in patient advisory boards. 3. Share experience on the use of treatment. 4. Participate in shared decision-making	1. Mobilize patient activism. 2. Partner with funders to address affordability. 3. Leverage on legal and legislative enablers to hold stakeholders accountable. 4. Raise funding to facilitate treatment access.
Healthcare provider/ healthcare facility	1. Conduct clinical studies and address physician knowledge gaps and beliefs 2. Develop treatment guidelines 3. Incorporate treatment into local treatment algorithms 4. Define treatment goals and outcomes	1. Evaluate the safety and efficacy of the treatment from clinical studies 2. Participation in shared decision-making 3. Acquire expertise and knowledge on the use of treatment 4. Educate patients and funders on new treatment	1. Task shift and educate providers and system to optimize access 2. Integrate haemophilia care into health care systems 3. Ensure the development of a diverse treatment portfolios 4. Prioritize an affordable operational research agenda
Public/private funder	1. Optimise gross national product allocated to treatment access 2. Undertake health technology assessment 3. Review and register treatment 4. Perform cost-effective analyses	1. Collect quality and credible data 2. Setup and regulate adverse event reporting system 3. Receive and action real-world use data 4. Review the risk-benefit profile of marketed products continuously	1. Provide specific funding for treatment 2. Prioritize policies aiming to reduce prices 3. Reduce prices of originator drugs 4. Identify and remove barriers to rare disease treatment access

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Treatment may be accessible, affordable and available but may not be implemented in routine practice. It is the responsibility of healthcare providers to facilitate the implementation of new therapies. The strategies to accomplish this are diverse and include (1) partnerships and collaborations with manufacturers, funders and patients; (2) education and advocacy activities across all stakeholders; (3) formulation and implementation of essential medicine lists in line with international guidelines; (4) through clinical research, evaluating and implementing of novel therapies to address the patient unmet needs.

The critical role of government funders is to provide a policy framework to guide the development of the treatment and the data evaluation and to provide funding commensurate with the benefit of the treatment. In both resourced and under-resourced settings, funders should be seen to be fair in allocating funds and applying funding principles. The United Nations resolution on rare diseases, which 193 governments supported, encourages Member States to foster the creation of networks of experts and multidisciplinary specialised expert hubs, interalia, for rare diseases and to increase research support by strengthening international collaboration and coordination of research efforts and the sharing of data while respecting and protection patient privacy.[21]

In addition to the role of various stakeholders, there is a need to put measures in place to maintain and sustain treatment access, as reflected in Figure 2. Sustainable treatment access requires additional considerations beyond the roles of individual stakeholders. These include initiatives to establish local research and develop capacity; establishing cost-effective manufacturing facilities; empowering health facilities to be optimally functional and accessible to PWH; provision of an optimal healthcare workforce to meet the treatment demands; community engagement for alignment, partnership and collaboration in raising funds and formulating policies to facilitate treatment access.[22]

3.2 | Improving the sustainability of treatment access

Holding each stakeholder accountable and implementing focused sustainability measures will result in positive patient outcomes and long-term health impacts. Realising these life-changing impacts will require a progressive mindset shift from individual stakeholder roles to patient-centred approaches. The latter entails optimising collaboration and partnerships with PWH in a shared decision-making approach.[23] In this context, shared decision-making aims to empower PWH, establish sustained engagement in their treatment, record and analyse their treatment experience, and systematically collate and analyse patient-reported outcomes. This can be accomplished through a holistic approach to healthcare access rather than a narrow focus on treatment access alone.

Access to optimal health care, defined as the timely use of personal health services to achieve the best health outcomes,[5] requires evaluating several aspects of health care delivery. These include the availability of specialised health care services, utilisation and removal of barriers to their use, relevance and effectiveness of the services in addressing the health care needs and equity of health care access.[24] The availability of health care services is often measured by the number of HCPs or facilities per capita, which varies widely among the global population of PwIBD. While the per capita use of FVIII and FIX clotting factor is well established,[7] the per capita availability of HCPs and facilities remains to be discovered. Even less known is how these healthcare services and workforce are used by PwIBD and the quality of the service delivered to them. Several factors, including personal and organisational barriers, influence access to and utilisation of health care services. Health equity is equal access and opportunity to remain healthy. Given the enormous geopolitical and economic inequity in health delivery, access equity remains a theoretical consideration rather than a practical issue in the bleeding disorders community.

4 | ONGOING CHALLENGES OF ACCESS TO TREATMENT FOR PEOPLE WITH VON WILLEBRAND DISEASE WORLDWIDE

In the past decade, there has been a surge of interest and research in von Willebrand Disease (VWD), culminating in the recent multi-society international guidelines on diagnosing and managing VWD.[25,26] In some respects, the issues facing people living with VWD (PwVWD) in lower-income settings are similar to those living with haemophilia: limited access to targeted factor replacement therapies, the use of alternative plasma-derived products, inconsistent supply and poor access to prophylactic treatment. However, these issues are magnified

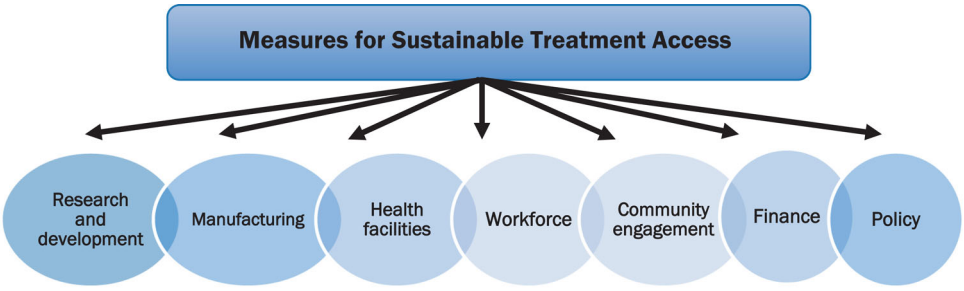


FIGURE 2 Measures to improve sustainable treatment access.

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for PwVWD as, even in high-income settings, we have only a single recombinant product available, specific VWF replacement therapies are not universally available, and reliance on products such as cryoprecipitate is still encountered.[27] In contrast to haemophilia, designing effective non-factor or gene therapy approaches for VWD has yet to be realised, so these issues will remain for the foreseeable future unless addressed.

4.1 | Challenges in the diagnosis of VWD

Internationally, awareness of VWD needs improvement, and the most significant barrier to accessing treatment for PwVWD is the absence of a diagnosis. In HIC, diagnostic delays for PwVWD are frequently encountered, particularly for females.[28–30] Despite the expected prevalence of 0.1%–1%, actual registration rates of PwVWD are much lower, with 2020 data identifying median registration rates in HICs of 45.1 per million population.[31–34] There is a considerable gap seen in lower and lower-middle-income countries (LIC/LMIC), with registration rates 100 times lower again (median 0.5–0.6/million population).[33] The representation of VWD types is inverted in lower-income settings, with type 2 and 3 VWDs dominating, compared to the majority of kind 1 VWD in HICs.[33,34] There remains a lack of data focused on VWD in LMIC/LICs, and we still need to adapt diagnostic and treatment algorithms to improve care in these settings. Internationally, the complexity and cost of VWD diagnostic assays continue to limit their availability and use. The current international VWD diagnostic guidelines are challenging to implement in a resource-limited setting, and consideration should be given to new, simplified approaches to stratify VWD diagnosis in this context. It is recognised that patients with VWD have varying responses to DDAVP, although past reports usually have also included extensive laboratory investigations to determine VWD type.[35] Responsiveness to DDAVP is a key metric in determining treatment for VWD-related bleeding or perioperative prophylaxis. There is the potential to simplify VWD diagnosis in resource limited settings, segregating according to DDAVP response rather than traditional VWD type. This simplified binary system of VWD (i.e., DDAVP responsive or requiring VWF replacement therapy) is currently under investigation by Federici et al., with initial findings presented at a 2023 WFH focused session on LMIC/LIC and due for publication soon.[36]

4.2 | Challenges with treatment of VWD

Treatment for PwVWD, where available, is often in response to bleeds or before the haemostatic challenge. Therapy is directed at boosting plasma VWF levels using either endogenous VWF release (prompted by DDAVP) or administration of exogenous VWF replacement (typically with plasma-derived or recombinant VWF therapy). For responsive patients, DDAVP has multiple routes of administration (intravenous, IV, subcutaneous, SC, or intranasal, IN), affording flexibility for patients and treatment centres. Adjunctive treatment using antifibrinolytics, such as tranexamic acid, is also an essential care component. Access and availability of haemostatic treatment products internationally remain an issue, particularly in resource-limited settings. National governments are often guided by the World Health Organisation's Model List of Essential Medicines, which provides a suggested minimum pharmacopoeia. While DDAVP, plasma coagulation Factors VIII and IX are included on this Essential Medicines list, specific VWF replacement therapies are still excluded, with only cryoprecipitate listed.[11] Following the WOMAN study, tranexamic acid was incorporated, but only in its intravenous form.[37,38] Even in countries where oral tranexamic acid is widely available, medicine shortages have been reported.[34] These issues, in combination with the global lack of intranasal DDAVP, severely limit treatment options for PwVWD internationally.[39] The WFH continues to advocate for the availability of treatment for these critical haemostatic treatments for PwVWD internationally and to raise awareness of these issues.[28]

A significant cause of morbidity for women with VWD is heavy menstrual bleeding (HMB) with resultant iron deficiency (ID) and iron deficiency anaemia (IDA). HMB is the most frequently reported and most severe bleeding symptom experienced by women with VWD.[40,41] For women who are not actively trying to conceive, hormonal therapy is the cornerstone of treatment to minimise HMB.[42] Hormonal therapy for HMB is often conflated with contraception, which, due to societal taboos or religious beliefs, may result in the rejection of an important therapeutic modality for women and girls. Healthcare providers must confront these concerns and provide culturally appropriate information to tackle taboos surrounding hormonal treatments. Otherwise, women and parents risk forsaking the benefit of hormonal therapies, further disadvantaging women and girls with VWD.

In stark contrast to haemophilia, the use of prophylaxis by people living with VWD is not routine, with both patient and physician acceptability of prophylaxis remaining challenging. The causes for this are multifactorial, including the normalisation of excess bleeding in VWD, the demands, frequency, cost and availability of regular intravenous prophylaxis in VWD and healthcare providers' attitudes regarding the need for prophylaxis in PwVWD. Compared to haemophilia, research into the role of prophylaxis in VWD is very limited, with only a single randomised placebo-controlled clinical trial available for the evidence base of the recent 2021 international guidelines, the rest being pre-post exposure studies.[25,43] These guidelines suggest that long-term prophylaxis should be used for PwVWD with a history of severe and frequent bleeding. This guidance was a significant step forward in improving access for PwVWD to prevention but still imposed a bleeding requirement on PwVWD. This is markedly divergent from the focus on early prophylaxis and joint protection for those with severe haemophilia. Improved funding, research, product choice and availability could alter attitudes and protocols for prophylaxis in VWD, but achieving these goals seems remote.

Given the phenotypic diversity of VWD, it may be easy to trivialise bleeding experienced by PwVWD. Still, these episodes hurt physical and psychological functioning as well as health-related quality of

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life.[29,41,44] With care for people with haemophilia improving exponentially, we must now direct efforts to advance our knowledge base and therapeutic options for PwVWD. Central to all improvements should be consideration of implementation in both high- and low-income settings to ensure equitable advances in care for all PwVWD.

CONFLICT OF INTEREST STATEMENT

JM has received research grant/research support from Biomarin, CSL, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, and Spark; has been a consultant/scientific board for Biomarin, CSL Behring, Novo Nordisk, Roche, Takeda, Sanofi and Spark; and has received speaker bureau from Novo Nordisk, Pfizer, Roche, Sanofi and Takeda

SD has no conflict to declare. M.L. has served on an advisory board for CSL Behring and as a consultant for Sobi, CSL Behring, Takeda and Band Therapeutics. She has received speaker fees from Sobi and Takeda and research funding from Takeda.

DATA AVAILABILITY STATEMENT

Not applicable to this paper.

ETHICS STATEMENT

This review did not require ethics approval.

ORCID

Johnny Mahlangu https://orcid.org/0000-0001-5781-7669
Saliou Diop https://orcid.org/0000-0002-2354-3839
Michelle Lavin https://orcid.org/0000-0003-2999-4216

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