

# Treatment adherence in hemophilia

Courtney D Thornburg<sup>1</sup>  
Natalie A Duncan<sup>2</sup>

<sup>1</sup>Hemophilia and Thrombosis Treatment Center, Rady Children's Hospital, San Diego, CA, <sup>2</sup>Indiana Hemophilia and Thrombosis Center, Indianapolis, IN, USA

**Abstract:** Prophylactic clotting-factor regimens reduce the occurrence of bleeding episodes and maintain joint health in individuals with moderate and severe hemophilia. However, these outcomes are only achieved with adherence to prescribed prophylaxis regimens. There are several types of barriers to adherence related to key patient, condition, treatment, health-care system, and/or socioeconomic variables. Notably, health-care professionals may not prescribe prophylaxis if they perceive that a patient will be nonadherent. Prophylactic treatment strategies should be developed with the patient and family, focused on individualized treatment goals. Personalized strategies are needed to reinforce the importance of and encourage confidence in administering the regular infusions required for prophylactic therapy. These strategies may include verbal and written information delivered by health-care professionals, peers, and interactive media. The advent of extended half-life clotting factors requiring less frequent infusion may improve adherence.

**Keywords:** hemophilia, prophylaxis, adherence, VERITAS-Pro

## Introduction

Hemophilia A and B are rare inherited bleeding disorders caused by deficiency of coagulation factor VIII (FVIII) and factor IX (FIX), respectively.<sup>1</sup> These disorders are characterized by recurrent bleeding episodes, primarily into the joints and muscles.<sup>2</sup> Over time, repeated joint bleeding damages the cartilage and bone, which ultimately leads to crippling arthropathy.<sup>1</sup>

Hemophilia is typically treated with coagulation-factor replacement administered either prophylactically, ie, to prevent bleeding episodes, or episodically (on-demand when bleeding occurs).<sup>3</sup> Prophylaxis is the preferred treatment regimen for patients with severe hemophilia (generally defined as <1% baseline clotting-factor activity), as it significantly reduces the frequency of total and joint bleeding events and substantially reduces the frequency of hemophilic arthropathy compared with episodic treatment.<sup>4-11</sup> Results from magnetic resonance imaging in the pivotal Joint Outcomes Study suggest that prophylaxis prevents chronic microhemorrhage into the joints, as well as clinically obvious hemarthrosis.<sup>4</sup> Furthermore, prophylaxis is associated with fewer work and school absences,<sup>12</sup> improved physical health-status scores, decreased pain, and higher health-related quality-of-life (QoL) scores (measured using either generic or hemophilia-specific questionnaires).<sup>10,13-15</sup> New evidence suggests that starting prophylaxis as early as possible, prior to joint bleeding, ensures the best efficacy.<sup>16</sup>

Prophylaxis may be initiated before or after onset of joint bleeding and joint disease. Primary prophylaxis has been defined as regular, continuous replacement therapy started in the absence of joint disease and before the second joint bleed and age 3 years; secondary prophylaxis as regular, continuous replacement therapy started before the onset of joint disease and after two or more joint bleeds; and tertiary prophylaxis

Correspondence: Courtney D Thornburg  
Rady Children's Hospital, 3020 Children's  
Way – MC 5035, San Diego,  
CA 92123, USA  
Tel +1 858 966 5811  
Email cthornburg@rchsd.org

as regular, continuous replacement therapy started after the onset of joint disease.<sup>17</sup> The continuous prophylaxis definition includes a requirement that the individual receive “a minimum of an a priori defined frequency of infusions for at least 45 weeks (85%) of the year”.<sup>17</sup>

In light of the demonstrated benefits of prophylaxis in hemophilia, the Medical and Scientific Advisory Council of the National Hemophilia Foundation recommends that prophylaxis begin at a young age,<sup>18</sup> prior to the onset of recurrent bleeding, in children with severe hemophilia A and B.<sup>18</sup> These guidelines suggest that prophylaxis should be given to target a trough FVIII or FIX level >1%. Notably, current guidelines do not provide a recommendation for prophylaxis in those with mild–moderate hemophilia; however, even infrequent bleeding events (eg, once or twice yearly) can lead to arthropathy,<sup>19</sup> and there is evidence to support the effectiveness of prophylaxis in this population.<sup>20</sup> There is no published guidance regarding the age at which to stop prophylaxis, although continued prophylaxis on an individualized basis may benefit adults with hemophilia.<sup>18,21–23</sup>

Given the improved outcomes associated with prophylaxis and the importance of adherence to these regimens in achieving these outcomes, this article reviews the current rates of adherence to prophylaxis regimens (with a focus on US-based studies), discusses barriers to adherence, describes the impact of treatment adherence on clinical and economic outcomes, and identifies approaches to improve health outcomes.

## Rates of prophylaxis prescription and usage

Despite the current recommendations and evidence base, prescription of prophylaxis for people with severe hemophilia is not universal.<sup>24</sup> Table 1 summarizes reported data on prophylaxis

rates over time. Primary sources include the Centers for Disease Control and Prevention (CDC) Universal Data Collection (UDC) program, the American Thrombosis and Hemostasis data set, and physician surveys.<sup>25–29</sup> Overall, prescription of prophylaxis has increased over time. Rates are highest in patients with severe hemophilia A and in the age range of 2–15 years.

Notably, in a 2003 global survey of hemophilia-treatment centers (HTCs; the International Hemophilia A Practice Patterns Survey), rates of hemophilia A prophylaxis prescription (sum of primary, secondary continuous, and secondary intermittent) in the US were lower than those reported for the UK, Canada, Australia, and Sweden. However, US rates were higher than those in a combined measure of other countries (including Belgium, Brazil, Finland, Hungary, Iceland, Israel, Japan, Malaysia, Mexico, the Netherlands, New Zealand, South Africa, Spain, and Taiwan).<sup>30</sup> In a follow-up Practice Patterns Survey in 2005 using the same questionnaire, the percentage of HTCs prescribing primary prophylaxis for severe hemophilia A had significantly increased in the US, from 19% in 2003 to 28% in 2005 ( $P < 0.0001$ ), with a corresponding decrease in on-demand treatment.<sup>31</sup> The proportion of clinicians prescribing secondary prophylaxis remained stable. A similar pattern was observed in the UK, with significantly increased use of primary prophylaxis for severe hemophilia A from 2003 (30%) to 2005 (38%) and generally stable rates of secondary prophylaxis during this time.<sup>31</sup> In both surveys, prophylaxis prescription was almost 100% in Swedish HTCs.<sup>30,31</sup>

## Treatment-adherence rates in hemophilia

A number of studies have measured adherence to prophylaxis in children and adults with hemophilia. Adherence is defined as the active, voluntary, and collaborative involvement of a

**Table 1** Adherence rates with continuous prophylaxis for patients with hemophilia over time

Data source	Type of study	Time frame	Rate of prophylaxis by disease severity (%)			
			Severe	Moderate	Mild	Unknown
CDC UDC program <sup>25</sup>	Observational prospective	1998–2004	A: 35.3 B: 27.1 A + B: 34	A: 13.4 B: 6 A + B: 11	A: 0.6 B: 0.7 A + B: 0.7	NA
CDC UDC program <sup>26</sup> Blanchette et al <sup>27</sup>	Observational prospective Survey of North American HTC clinicians*	2005–2009 2002	A + B: 48 A: 47 B: 30 A + B: 44.2	A + B: 16.2 A: 13 B: 3 A + B: 12.9	A + B: 2.1 A: 0 B: 0 A = B	A + B: 27.8 NA
Zappa et al <sup>28</sup>	Survey of North American HTC clinicians	2010	A: 58 B: 51 A + B: 56.8	NA A + B: 12.9	NA A = B	NA
ATHN data set <sup>29</sup>	Registry	2010–2015	A: 67.6 B: 60.7	A: 30.1 B: 14.1	A: 4.4 B: 4.5	A: 7.5 B: 6.2

**Note:** \*Patients aged ≤18 years only.

**Abbreviations:** CDC, Centers for Disease Control and Prevention; UDC, Universal Data Collection; NA, not applicable; HTC, hemophilia-treatment center; ATHN, American Thrombosis and Hemostasis Network; A, FVIII deficiency; B, FIX deficiency.

patient in a mutually acceptable course of behavior to produce a desired preventive or therapeutic result.<sup>32</sup> In clinical research, adherence is generally quantified by the number of doses of medication administered compared with the number of doses prescribed. Definitions of acceptable adherence differ substantially across studies. In general, across disease states, excellent adherence is commonly but arbitrarily defined as administering at least 75%–80% of doses/medication.<sup>24,33–36</sup> Measures of treatment adherence also vary widely in clinical practice and clinical study reporting,<sup>34,37,38</sup> and may include data from the review of treatment logs, pharmacy records, bleed frequency (including joint bleeds), school attendance, and participation in physical activity/sports.<sup>24,39</sup> All these methods are subject to inherent bias and confounding factors, and a combination of methods is required to assess adherence accurately. Also, few measures capture all the elements of adherence. For example, a patient may infuse the correct dose on the recommended days of the week, but infuse in the evening rather than the recommended morning. This patient could be considered partially adherent.

In hemophilia-adherence research, a measure called the VERITAS-Pro (Validated hEmophilia-RegImen Treatment-Adherence Scale – Prophylaxis) was developed and validated to provide a standardized method for evaluating adherence to prophylaxis. The VERITAS-Pro consists of 24 questions utilizing 5-point Likert scales, with total scores ranging from 24 (most adherent) to 120 (least adherent). In addition to producing a total adherence score, questions are divided into six subscales (time, dose, plan, remember, skip, and communicate) to delineate the areas of nonadherence, such that this scale addresses the details about the quality of adherence. The primary infuser (patient or caregiver) completes the scale. The VERITAS-Pro has been translated into more than 30 languages. It provides clinicians the opportunity to tailor interventions to improve patient adherence using individualized patient-reported information about specific issues underlying nonadherence.<sup>40</sup>

## Patient-reported adherence

Patient-reported adherence rates from patient surveys, pharmacy logs, and infusion logs are shown in Table 2. Overall, reported adherence is highest in young children. For example, a US-based study evaluated adherence to prophylaxis using the VERITAS-Pro and found that pediatric patients (n=47) reported significantly better adherence compared with adults (n=23), with scores of 38 and 45.8, respectively ( $P<0.05$ ).<sup>41</sup> In accordance with this result, a second study, including adults with moderate or severe hemophilia and caregivers of children with moderate or severe hemophilia, was conducted in the US, Canada, and Australia (110 total respondents).<sup>43</sup> Mean VERITAS-Pro scores of 39.6 and 50.8 were reported by caregivers of children with hemophilia and by adults with hemophilia, respectively ( $P<0.001$ ).<sup>43</sup>

## Health-care provider adherence assessments

Two studies evaluated health-care provider-reported rates of adherence to prophylaxis. Surveys published in 2008 and 2012 conducted with HTC clinicians employed similar questionnaires and defined adherence as administration of  $\geq 80\%$  of the prescribed number of infusions to children with hemophilia. In the 2008 survey (n=59), 54% of clinicians perceived that  $>75\%$  of patients met the adherence criteria; in the 2012 survey (n=48), this number had fallen to 42% of clinicians.<sup>24,35</sup>

A 2010 survey of US HTC nurses conducted as part of the Practice Patterns Survey identified varying definitions of adherence used in clinical practice: no breakthrough bleeds (except for trauma situations), no deterioration in joint health, and patients following the physician's prophylaxis prescription.<sup>28</sup> Adherence was defined as reported prophylactic doses per month divided by prescribed prophylactic doses per month. Eighty percent and 78% for severe hemophilia A and B, respectively, achieved this criterion. Estimated

**Table 2** Patient-reported rates of adherence with prophylaxis

Reference	Data source	Age	Definition of adherence	Reported adherence
31	Survey	1–18 years	$>75\%$ of prescribed infusions	58.8% adherent
32	Survey	Children and adults	$>80\%$ of prescribed infusions	73% adherent
41	VERITAS-Pro	Adolescents	Score of $\geq 57$	30% adherent
42	Pharmacy logs	Children and adults	Days supply/days observed $\geq 60\%$	Adherence achieved 50% of the time
36	Infusion logs	Children and adults	$>67\%$ weeks of prophylaxis	Children: 26 Adults: 39
37	Infusion logs	Adults, 18–56 years	Study scoring system to rate adherence with frequency and dosage	Median adherence to frequency: 76% Median adherence to dosage: 93%
4	Randomized controlled trial, infusion logs	6 months–6 years	Not defined	Mean adherence 96%; 2 of 32 had difficulty with infusion schedule

adherence was highest among those aged  $\leq 2$  years (90%) and lowest among those aged 18–24 years (64%).<sup>28</sup>

Physician-prescribing patterns and perceptions of adherence to prophylaxis are likely interrelated. In a physician survey, 34% reported that in the last year, they had not prescribed prophylaxis for some people with hemophilia (PWH), due to concerns about nonadherence.<sup>35</sup> Walsh and Valentino also reported that nonadherence was a reason for modifying the treatment regimen in 32% of subjects.<sup>44</sup>

## Barriers to treatment adherence

Barriers to adherence to prophylaxis have been reported by patients, caregivers, and health-care providers (Table 3). There are five key types of adherence barriers: patient-related factors, condition-related factors, treatment-related factors, health-care system factors, and socioeconomic factors.

### Patient-related factors

Patient health beliefs relate strongly to adherence. Health beliefs influence the acceptance of the diagnosis and understanding of disease consequences and the benefits of a given therapy. The effect of health beliefs on the likelihood of adherence is described by the health-belief model.<sup>47</sup> An individual’s perception of susceptibility to illness, severity of the consequences of illness, and belief in the potential of treatment to reduce the consequences may play a role in adherence.<sup>48</sup> For example, the likelihood that patients with

severe hemophilia A will administer prophylactic infusions depends on the perceptions that they are susceptible to joint bleeds, which will lead to chronic arthropathy, and that infusions will prevent these complications. The impact of these basic perceptions on treatment adherence is modified by many other factors, including such barriers as time constraints, venous access, and cost.

Schrijvers et al found that adherence depends on patient acceptance of hemophilia, feeling or fearing the symptoms of hemophilia, and having planning skills to implement prophylaxis.<sup>57</sup> The authors suggested that adherence varied in different subgroups, ranging from best to worst adherence: 1) prophylaxis is integrated into life, 2) prophylaxis is according to physician advice, struggling with irregular situations, 3) prophylaxis is too much to handle, and 4) prophylaxis is a confrontation with illness.

Other patient-related factors are previous illness experience, previous adherence history, comorbidities, cognitive impairment, and mental illness, including depression.<sup>49</sup> Age is also an important modifying factor. Young children and the elderly depend on others for appropriate medical care, whereas adolescents, young adults, and middle-aged adults are typically independent. Social concerns play a large role, especially among adolescents who want to fit in with their peers and be unbothered by illness.

Young adult PWH (YA-PWH) are at high risk of discontinuing prophylaxis and poor adherence. This is at least partially attributable to the numerous changes that occur during this time, including transferring care from pediatric to adult health-care systems and assuming responsibility for medical care.<sup>42,58</sup>

Quon et al summarized these key unmet challenges for young adults with hemophilia:

The need to proactively establish responsibility for health care decisions with diminishing family influence; unfamiliarity with adult HTC providers and policies, coupled with the loss of access to pediatric health care providers with whom YA-PWH have developed long-standing relationships; and an unconvincing value proposition of regular adult HTC visits in the age of prophylaxis.<sup>59</sup>

These barriers and challenges are concerning, since bleeding rates increase in adolescents and young adults who discontinue prophylaxis.<sup>44</sup>

### Condition-related factors

Condition-related factors include duration and severity of illness. For example, medication adherence may be high

**Table 3** Barriers to prophylaxis adherence and potential strategies for addressing these barriers

Barriers to adherence <sup>28,31,42,45–49</sup>	Potential strategies to improve adherence <sup>50–56</sup>
<ul style="list-style-type: none"> <li>• Patient-related factors                             <ul style="list-style-type: none"> <li>◦ Health beliefs</li> <li>◦ Age</li> </ul> </li> <li>• Condition-related factors                             <ul style="list-style-type: none"> <li>◦ Frequency of bleeding</li> </ul> </li> <li>• Treatment-related factors                             <ul style="list-style-type: none"> <li>◦ Venous access</li> <li>◦ Dosing regimen</li> <li>◦ Cost</li> <li>◦ Perceived costs</li> </ul> </li> <li>• Health-care system factors                             <ul style="list-style-type: none"> <li>◦ Access to hemophilia-treatment center</li> <li>◦ Insurance</li> </ul> </li> <li>• Socioeconomic factors                             <ul style="list-style-type: none"> <li>◦ Language</li> <li>◦ Acculturation</li> <li>◦ Health literacy</li> <li>◦ Balancing the child’s care with other family and social needs</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Education (multimedia, peer-to-peer mentors, tailored to patient’s primary language, development, and health literacy)                             <ul style="list-style-type: none"> <li>◦ Benefits of prophylaxis</li> <li>◦ Venous access</li> <li>◦ Health-care navigation</li> <li>◦ Patient portals in ehealth records</li> </ul> </li> <li>• Monitoring                             <ul style="list-style-type: none"> <li>◦ Logs</li> <li>◦ Mobile direct observation</li> </ul> </li> <li>• Reminders                             <ul style="list-style-type: none"> <li>◦ Text messaging</li> <li>◦ Phone app</li> </ul> </li> <li>• Incentives (age-appropriate)                             <ul style="list-style-type: none"> <li>◦ Reward charts</li> <li>◦ Financial</li> </ul> </li> </ul>

initially but wane over time, particularly if the patient becomes asymptomatic. An international survey of patients and nurses identified infrequent bleeds as the greatest barrier to adherence.<sup>30</sup> Patients experiencing few bleeds or who do not recognize bleeds may perceive lower susceptibility to illness or underestimate the severity of consequences of illness.<sup>42,60</sup> This is especially true for patients who started prophylaxis at a young age and may not have experienced bleeding events or their consequences.<sup>50</sup> Children who are on prophylaxis must be taught what a bleed feels like, so they can recognize and treat breakthrough bleeding as soon as possible. Patients and caregivers should also be educated that prophylaxis likely prevents microbleeds and is thus critical, even when patients are asymptomatic.<sup>4</sup>

### Treatment-related factors

Complex regimens based on dosage frequency, dosage amount, form of drug, and delivery method can interfere with adherence. In a survey of US children and adults receiving prophylaxis for hemophilia A or B, those who reported excellent or less-than-excellent adherence identified the time-consuming nature of their prophylaxis regimen as the most important adherence barrier.<sup>33</sup> Prophylaxis regimens typically involve two to four infusions per week, each taking 2–>50 minutes, depending on the clotting-factor formulation and preparation required.<sup>18,61</sup> It is difficult for many parents of children with hemophilia to fit such a time-intensive regimen into their morning routines and still arrive at school and work on time.<sup>61</sup>

Perceived harm and risks may interfere with adherence. Parents commonly cite difficulty with venous access or “sticking” the child as an adherence-related challenge.<sup>31</sup> Venous access issues are often most distressing for the youngest patients: one Japanese study reported this as the most important barrier to adherence in children aged <5 years.<sup>62</sup> In a 2006 international survey, other important concerns of nurses, patients, and caregivers included the risk of infection and thrombosis associated with venous administration, and an inability to maintain the intravenous line; 39% of nurses identified the potential risks associated with plasma-derived products as a barrier to prophylaxis. Since utilization of plasma-derived products is relatively low in the US, this barrier is not significant there.<sup>30</sup>

Cost of treatment is frequently cited as a critical challenge to prophylaxis adherence in hemophilia. Although prophylaxis is cost-effective in comparison with episodic treatment, the overall cost is high.<sup>63,64</sup> In the 2006 survey just cited, 45% of nurses from all countries identified cost

concerns as a significant barrier to prophylaxis, a particular issue for US-based nurses.<sup>31</sup> Reported estimates of the cost of prophylaxis vary according to factors including study date, disease severity, and inhibitor status. Few estimates based on US care and insurance systems have been published. In the landmark 2007 US study by Manco-Johnson et al,<sup>4</sup> it was estimated that for a 50 kg child with severe hemophilia A, the annual cost of prophylaxis could reach \$300,000 (2007 prices). In a 1995 US study, the estimated annual cost of prophylaxis in an adult with severe hemophilia A and no arthropathy or inhibitors was \$69,656.<sup>65</sup> A 2010 European study estimated the average lifetime cost of severe hemophilia A at €166,168,643.<sup>63</sup> In all these studies, the vast majority of the cost was accounted for by clotting-factor consumption. Because clotting-factor dose is based on body weight, the cost of the clotting factor will be increased in overweight or obese individuals.<sup>66</sup> It is estimated that ~30% of patients with hemophilia in the US are uninsured or underinsured (although this figure may change with the evolving US health-care landscape). Out-of-pocket costs for insured and uninsured patients may cause them to forgo medication doses or prophylaxis entirely.<sup>67</sup> The economic downturn of recent years also had an impact on adherence to prophylaxis, with patients skipping/reducing clotting factor doses or skipping prescription refills.<sup>68</sup>

### Health-care system factors

Health-care system factors include access to care (distance to HTC) and access to factor (insurance, need for prior authorization). As adolescents transition to adult care, they may experience difficulty navigating the health-care system and maintaining health insurance, and in turn have decreased adherence to prophylaxis. Adolescents who move away to college are at high risk of poor outcomes. In college, adolescents and young adults need to assume many new roles, such as performing self-infusions (if not started at a younger age), managing clotting-factor refills and storage, remembering the prophylaxis schedule, keeping track of appointments, and understanding medical insurance. Relationships with the HTC team may impact adherence as well. Tran et al showed that trust in the physician was associated with improved adherence.<sup>49</sup>

### Socioeconomic factors

Socioeconomic factors include family size, family structure, social support, income/insurance, health literacy, language, and culture. These factors affect the family’s ability to understand the disease and disease consequences and how to take

the medication. Family or cultural norms may affect patient willingness to accept treatment recommendations.

## Impact of treatment adherence on outcomes

The established benefits of prophylaxis compared to episodic treatment with regard to decreases in bleeding events (including joint bleeds) and joint damage, and improved QoL<sup>4-13</sup> are dependent on adherence to prescribed regimens.<sup>38,69,70</sup>

A recent study assessed the relationship between adherence to prophylaxis, as measured by the VERITAS-Pro, and annual bleeding rate (ABR).<sup>71</sup> In the poor-adherence group, a higher proportion of subjects experienced one or more bleeds annually than those in the good-adherence group (86% vs 62%). A separate 2014 survey of 55 adults with hemophilia and 55 caregivers of children with hemophilia also correlated poor adherence (again measured using the VERITAS-Pro) with increased self-reported breakthrough bleeding and target joint bleeds in the preceding year.<sup>43</sup> A cohort study of 44 patients with severe hemophilia A demonstrated that increasing time with <1% FVIII-activity level was associated with increased bleeding events and hemarthrosis.<sup>69</sup> Time spent at <1% was affected by adherence; patients with low adherence rates experienced more bleeds. Therefore, adherence to a prophylactic regimen may reduce the frequency of bleeding events. Another cohort study of 49 patients with severe hemophilia demonstrated that patients receiving prophylaxis who discontinued treatment of their own accord for varying periods generally had a greater number of joint bleeds and higher scores on the Pettersson scale, indicating more severe arthropathy.<sup>70</sup>

Other studies have demonstrated a relationship between adherence to prophylaxis and pain. In US adults and children with hemophilia using high-intensity treatment regimens (including prophylaxis), greater adherence was associated with better bodily pain scores on a QoL measure compared with lower adherence.<sup>38</sup> A more recent US study confirmed an inverse relationship between treatment adherence and chronic pain in adolescents and young adults with moderate or severe hemophilia.<sup>72</sup>

Adherence to prophylaxis may also affect economic outcomes, including direct treatment costs and indirect costs, such as those due to work/school absenteeism. A 2014 survey found that poor adherence was associated with more missed school days among children with hemophilia.<sup>43</sup> Overall, studies have suggested that prophylaxis is cost-effective.<sup>63</sup> Finally, Iorio et al developed a model to predict ABR, comparing prophylaxis with standard half-life products to

extended half-life products at different adherence levels. ABR was lower with extended-half life products at each adherence level.<sup>73</sup>

## Expert opinion

### Strategies to address adherence to prophylaxis

Strategies are needed to align prophylaxis recommendations with patients' goals and skills. Types of interventions may include educational, cognitive/behavioral, and skill training (Table 3). These approaches need to account for individual patient factors, such as age, developmental stage, prior hemophilia history, comorbidities, mental illness, and socioeconomic status. For example, strategies to increase adherence in the youngest patients must target caregivers responsible for treatment administration, whereas strategies for adolescents and adults will target patients directly. It is especially important to create strategies targeting adolescents, as they become increasingly independent and take on responsibility for self-care, including factor infusions.<sup>74-76</sup> The National Hemophilia Foundation Steps for Living program has excellent resources for 18- to 25-year-olds.

Providers need to work closely with patients to understand their needs and promote adherence. The British Columbia Hemophilia Adult Team recommends that providers de-emphasize adherence as a primary goal and instead focus on the patient, developing customized treatment based on his/her priorities. Allowing the patient to design the treatment plan with the medical team may improve adherence.<sup>51</sup> Patient navigators can also help patients adhere to a prophylaxis regimen by helping them attend appointments, maintain insurance, and obtain clotting-factor refills. Patient navigators have a critical role when patients transfer between health-care teams.

Because belief in treatment necessity is a motivator for treatment adherence, repeated education is an important strategy for improving adherence in hemophilia. Indeed, health literacy has been positively associated with adherence, and health-literacy interventions increase both health-literacy and adherence outcomes.<sup>77</sup> Education can occur via written/verbal communication during clinic visits and potentially through such programs as peer-to-peer mentoring. Education should be tailored to the patient's primary language, development, and current health literacy, avoiding jargon and complex details. Educational content should include the reason for the medication, expected duration, expected response, side effects, monitoring, how to obtain medication, and how to take the medication.

In addition to interventions to improve health literacy, other socioeconomic barriers to adherence to prophylaxis in hemophilia may be best addressed by the HTC social workers or other psychosocial support personnel. Identifying the sources of family financial support, obtaining family support in administering a medication, offering emotional support, encouraging family cohesion, helping the patient's mother to develop a realistic perception of disease severity, supervising medication administration, and assisting patients to find health insurance have been identified as socioeconomic variables having a positive effect on adherence.<sup>78</sup> For YA-PWH, additional strategies may include educating HTC staff about the challenges of transition and transfer of care: improving education among adolescents such that YA-PWHs are prepared for the challenges of young adulthood, educating YA-PWH about the utility of regular comprehensive care, and increasing access to care for patients who live remotely or work or attend college during the day.<sup>59</sup>

Motivational techniques may be implemented to improve self-care.<sup>52</sup> Providers can teach parents communication strategies to motivate children to take part in their health care and decision-making, going beyond simple illness management to a broader scope that allows autonomy and encourages children to take responsibility for their own health and risk behaviors.

Behavioral strategies to increase the feasibility of peripheral infusions can make administering clotting factor less daunting. Support and education can help young patients become self-sufficient in this technique, which may give them a sense of achievement and confidence in dealing with problems.<sup>71</sup> Hemophilia summer camp is an important venue for formal education, as well as peer-to-peer education and motivation regarding home therapy and development of the independence and confidence necessary for self-infusion.<sup>61,79</sup>

Electronic media are also useful in the delivery of educational content regarding hemophilia care and adherence. In a study of adolescents with hemophilia, an interactive website was developed specifically for teenagers with hemophilia to assist in transition from pediatric to adult care.<sup>54</sup> Content included hemophilia-specific education, self-management strategies, images, interactive animations, videos with health-care professionals, quizzes, and a glossary. User feedback was positive, with a significant change from baseline in self-efficacy and transition preparedness; the specific effect on adherence was not reported.<sup>55</sup>

Additionally, mobile-device apps on smartphones can send prophylaxis reminders to patients and provide

encouragement.<sup>56</sup> Electronic logs aid health-care providers in real-time recognition of nonadherence and in targeting strategies for improving adherence. Patients and providers can also use resources within electronic health records, eg, patient portals, to communicate about prophylaxis.

New technologies in the treatment of other chronic and long-term conditions may be applied to PWH. Direct mobile observation of treatment in patients with tuberculosis has been accomplished by having treatment supporters record mobile-phone videos of patients taking their medication.<sup>80</sup> The videos were reviewed by health-care professionals, who then responded with motivational and educational text messages to the patients. The majority of study participants preferred this to in-person visits with health-care professionals. Such an approach could be adopted for hemophilia patients administering home infusions, allowing them to ask their clinician questions during the interaction.

The use of financial incentives has been shown to enhance adherence in subjects requiring warfarin therapy. Daily reminders were sent from an electronic monitoring system, and adherence was measured with the international normalized ratio (INR) for warfarin. The incentive to take warfarin correctly was entry into a daily lottery with the chance of winning cash prizes. During the study, the number of pills taken incorrectly decreased significantly and the time out of INR range significantly reduced.<sup>81</sup> Such an approach might be considered in patients with hemophilia.

## Potential impact of new therapies on adherence

Patients typically infuse standard FVIII products three to four times per week for prophylaxis.<sup>18</sup> New extended half-life FVIII products are infused approximately one to two times per week.<sup>82,83</sup> Similarly, patients typically infuse standard FIX products two to three times per week for prophylaxis.<sup>18</sup> New extended half-life FIX products are infused once every 1–2 weeks. Intravenous administration is a key barrier to prophylaxis; the development of factor and non-factor-replacement products given subcutaneously may increase prescription of and adherence to prophylaxis.

Development of new clotting-factor products that reduce dosing frequency has the potential to enhance adherence and patient acceptance of prophylaxis by reducing the infusion-schedule burden. However, as with all treatment regimens, the patient's new infusion schedule should be simple to implement and acceptable to the patient. While many patients adapt well to new infusion schedules, some patients may have difficulty transitioning from infusing Monday, Wednesday,

and Friday, eg, to every fourth or fifth day. In these situations, new strategies to promote adherence and provide dosing reminders (eg, mobile-phone apps) may be helpful.

Prophylaxis regimens that allow for less frequent infusions may mitigate difficulties with venous access and time constraints. It may be possible for young children to receive prophylaxis via peripheral infusion, and ports may be discontinued at a younger age when infusions are less frequent. Alternatively, patients may agree to prophylaxis if they perceive that they will have “better protection” with the new products. Increased physical activity and improved QoL are the important patient outcomes that have been shown with new, extended half-life factors.<sup>84–86</sup> The availability of new factor products also provides clinicians new opportunities to educate patients and families about the benefits of prophylaxis.

## Summary

In summary, prophylaxis is proven to improve health outcomes in patients with hemophilia. There are several barriers to adherence to prophylaxis. Therefore, clinicians should identify and mitigate potential barriers at the onset of therapy, and continuously monitor for decreased adherence. Strategies to improve adherence should be used with patients who are at risk for or have poor adherence. Extended half-life factor products and subcutaneous administration of prophylaxis have the potential to decrease the burden of prophylaxis and improve adherence, ultimately resulting in improved health outcomes.

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## Author contributions

All authors contributed to the development of this review article, revised the paper critically, and approved the submitted and final versions.

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