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## HTC CME NetWorkShops™: Current Issues and Trends in Hemophilia Care

March 2, 2011

### Introduction

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The Blood CME Center recently launched an interactive program on clinical challenges in hemophilia treatment centers (HTCs). Participating HTCs across the United States hosted a series of live workshops that were also conducted via the Internet among off-site participants. The program goal for this activity, *HTC CME NetWork Shops™: Clinical Challenges in Your Hemophilia Treatment Center*, was to provide an expedient way for HTC staff to discuss the latest developments in hemophilia care by way of abstracts and posters from recently held hemophilia congresses, as practitioners do not always have the opportunity to view such materials firsthand and participate in discussions with experts about them.

A faculty steering committee comprising 4 noted experts in hemophilia, Prasad Mathew, MD; Margaret Ragni, MD; Michael Recht, MD, PhD; and Guy Young, MD, oversaw the selection of abstracts and posters for inclusion in the activity. The presenting faculty included Steven Pipe, MD; Leonard Valentino, MD; and Christopher Walsh, MD, in addition to Drs. Mathew, Recht, and Young. The end result of the NetWorkShops™ is an endeavor that documents key trends and issues within the scientific community concerning the nature and treatment of hemophilia. Supplemental expert commentary offered by steering committee members, other noted hemophilia experts, and lead authors of selected posters and abstracts provides further insights.

### Inhibitor Development

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Inhibitor development remains the most serious complication of hemophilia A in developed countries<sup>1,2</sup> and makes more difficult the treatment of bleeding episodes in both hemophilia A and hemophilia B.<sup>3</sup> While the incidence of inhibitors in hemophilia B is low compared to that in hemophilia A, hemophilia B patients with inhibitors experience greater morbidity due to the frequency of allergic reactions that often co-occur with the development of neutralizing antibodies to factor IX (FIX).<sup>4</sup> Although the potential for inhibitors cannot be predicted with accuracy, the development is believed to be multifactorial, involving both patient- and treatment-related factors, such as disease severity and genotype, genotype-immunogenotype interaction, ethnicity, timing and, in the case of hemophilia A, intensity of factor VIII (FVIII) exposure and FVIII product type.<sup>2</sup>

#### *Patient-Related Risk Factors: Genetics*

Within the past 2 decades, major advances in genetics and immunology have fostered a greater understanding of inhibitor development. Adding to this growing body of knowledge are contributions from several research teams involved in examining immunogenetics and the role of haplotypes. In their pivotal study of genetic factors associated with inhibitor development in hemophilia A, Astermark and colleagues provide [Initial Results From the Hemophilia Inhibitor Genetics Study \(HIGS\) Combined Cohort](#). This combined cohort study tested the hypothesis that antibody development to FVIII is mediated by immune-response genes. Clinical and laboratory data for 680 patients with hemophilia A, which included data for white patients (81%), as well as for Hispanic patients (8.8%), patients of African descent (6.2%), and other races and ethnicities (4%), were examined and subsequent genotyping of 14,626 single nucleotide polymorphisms (SNPs) from 1081 candidate genes was conducted to identify an association with inhibitor status. Although analyses are ongoing, and no definitive conclusions

currently may be drawn, investigators determined that 114 SNPs are associated with inhibitor status at the  $P < .01$  level, and functional pathways involved in a variety of cellular processes may be integral in inhibitor development.<sup>5</sup>

Two separate follow-up studies, one conducted by Howard and colleagues and the other by Schwarz and colleagues, specifically examined the *F8* haplotype in association with inhibitor status and race. [The Role of Immune-Response Gene Variants in Inhibitor Development in Black Patients With Hemophilia A](#) attempted to account for the greater frequency of inhibitors in patients of African descent compared to white patients. The Howard study team evaluated allelic distribution and influence of immune response gene variants on inhibitor development in 78 black patients with hemophilia A. PCR and genomic DNA were used to genotype SNP in TNF $\alpha$  promoter and CA-dinucleotide repeat polymorphism in the IL10 promoter. Analyses for genotype-specific associations with inhibitor status were performed with and without controlling for background *F8* haplotype.<sup>6,7</sup>

Investigators found no obvious association between inhibitor risk and genotypes containing the IL10 risk allele after controlling for background *F8* haplotypes, nor was there an association observed between inhibitor development and TNF $\alpha$  genotypes containing the risk allele identified in the study population.

Similar conclusions were reached by the Schwarz team of investigators, who examined [F8 Haplotype and Recombinant Product Use in Factor VIII Deficiency](#). This combined cohort study comprising data from HIGS (Hemophilia Inhibitor Genetics Study), MIBS (Malmö International Brother Study), and HGDS (Hemophilia Growth and Development Study) not only examined the role of haplotype in association with inhibitor development, but the effect of recombinant product type as well. Using self-reports and genetic determinants, investigators analyzed *F8* haplotype and inhibitor status and were unable to find a significant association. Moreover, no association was found between haplotype, recombinant product type, and inhibitor development.<sup>7</sup>

#### *Treatment-Related Risk Factors: Intensity of FVIII Exposure*

Various environmental factors are thought to influence the development of inhibitors. It is currently held that such factors, including timing and intensity of factor exposure, can affect genetic predisposition to inhibitor development.<sup>8</sup> Kempton and colleagues recently conducted a case-control study of [Risk Factors for Inhibitor Development in Mild and Moderate Hemophilia A](#) to shed light on a patient population for which data on inhibitor development are lacking by assessing the role of intensive exposure to FVIII on inhibitor formation. In the final analysis, 36 cases and 62 controls were examined, and the median age of subjects was 31 years. The distribution of subjects having <50, 50-100, or >100 prior exposure days was similar between groups, and 50% of cases had received intensive treatment with FVIII compared to 17.7% of controls. After multivariate adjustment, intensive treatment with FVIII remained strongly associated with inhibitor formation in patients with mild or moderate hemophilia A, and the risk appeared to be greater in adults  $\geq 30$  years.<sup>9</sup>

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## Treatment Strategies

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### *Immune Tolerance Induction*

For inhibitor patients, the best treatment option is eradication of the inhibitor through immune tolerance induction (ITI). This treatment is effective for approximately 70% to 85% of patients with hemophilia A and 30% of patients with hemophilia B.<sup>4,10</sup> Success is based on negative Bethesda titer and normal factor pharmacokinetics.<sup>10</sup>

Amy Dunn and a team of investigators at the Aflac Cancer Center in Atlanta, Georgia, attempted to characterize outcomes of [Immune Tolerance in Patients With Hemophilia A and Long-standing Inhibitors](#) who had poor risk features. By way of a chart review of 9 patients who had undergone ITI using recombinant FVIII, treatment predictors and response were analyzed. Most patients (78%) were of African descent and 44% had a family history of inhibitors. Based on the chart review and number of patients (4) who were successfully tolerized using ITI, the treatment can be considered in patients with long-standing inhibitors and other previously considered poor predictive features (see [Table 1](#)).<sup>11</sup>

**Table 1. Patient Outcomes**

Patient #	Time (m) to Tolerance or IT	Age When Started IT (years)	Inhibitor Titer (BU) @ Start of Late IT	Current Inhibitor Titer (BU)	Bleeding Episodes Responsive to Factor VIII	% FVIII Recovery
1	16	5.3	13	0	Yes (T)	114%
2	6.3	13.3	0	0	Yes (T)	112%
3	29	33	1.2	<1 (negative for lab)	Yes (T)	108%
4	15	55	<1	1.6	Yes (PT)	23%
5	25	28.4	14.9	0.6	Yes (PT)	55%
6	14	17.7	1.4	0	Yes (T)	85%
7	29	10.7	4.8	1.7	No	Not performed
8	11	18.8	5.4	25	No	3%
9	8	17.4	18.7	4.2	No	21%

From Dunn AL, et al. Poster presented at: 22nd Congress of the International Society on Thrombosis and Haemostasis; July 11-16, 2009; Boston, MA.

### *FVIII Concentrates*

Although several therapeutic options exist for the management of bleeding episodes in hemophilia patients, none can guarantee the same good outcome as specific FVIII or FIX replacement therapy, which traditionally has been used for noninhibitor patients and patients with low-responding inhibitors.<sup>10</sup> However, type of factor concentrate administered, plasma-derived or recombinant, has become a controversial issue of treatment-related risk factors for inhibitor development.<sup>1</sup>

In light of the controversy, Kruse-Jarres and colleagues conducted a safety review of the plasma-derived FVIII concentrate Alphanate® to address [The Ethical Concern About Using Plasma-Derived Factor VIII Concentrates in the US for the SIPPET Study](#). The SIPPET (Survey of Inhibitors in Plasma-Product Exposed Toddlers) study was recently launched to compare the inhibitor incidence in recombinant versus vWF-containing FVIII in previously untreated patients (PUPs). However, perceived infectious risks associated with use of a plasma-derived product have become a barrier to study enrollment in the United States. Kruse-Jarres and investigators compiled a safety profile of the agent, in the process reviewing donor processing, viral testing, and purification steps involved with fractionation. To date, no confirmed cases of HIV, HBV, or HCV have been reported in connection with use of Alphanate®. Investigators determined that enrollment in studies such as SIPPET are ethical, but clinicians have a responsibility to understand the safety profile of FVIII concentrates.<sup>12</sup>

Examining factor concentrate use from another angle, Walsh and Valentino conducted a survey of HTC to elucidate practice and outcomes data concerning [Factor VIII Prophylaxis for Adult Patients With Severe Hemophilia A](#). Prophylaxis is now considered an optimal treatment modality for patients with severe hemophilia A.<sup>13</sup> The Walsh and Valentino study adds to the growing knowledge concerning prophylaxis since publication of the pivotal Manco-Johnson study in 2007, which decisively established the benefits of prophylaxis for preventing bleeding episodes and joint damage.<sup>14</sup>

Of 23 surveys sent to US HTCs, 10 were completed, with data collected on approximately 145 patients. There was unanimous agreement that prophylaxis is appropriate in certain adults with hemophilia A. Anticipated poor adherence and cost are perceived as the greatest barriers to its use in adults. Survey findings also suggest that prophylaxis prevents bleeding in this patient cohort and discontinuation of treatment is associated with increased bleeding events.

### *Bypassing Therapy*

Numerous studies have documented the safety and efficacy of activated prothrombin complex concentrates (aPCCs) and recombinant factor VIIa (rFVIIa), bypassing agents used for the treatment of patients with severe hemophilia and inhibitors.<sup>3,15-18</sup> Nevertheless, dosing and efficacy of the bypassing agents have not been fully established.

### rFVIIa

Valentino and colleagues utilized [Hemophilia and Thrombosis Research Society \(HTRS\) Registry Data for Specific Joint Bleeds in Hemophilia](#) to understand the effectiveness and safety of rFVIIa, thereby

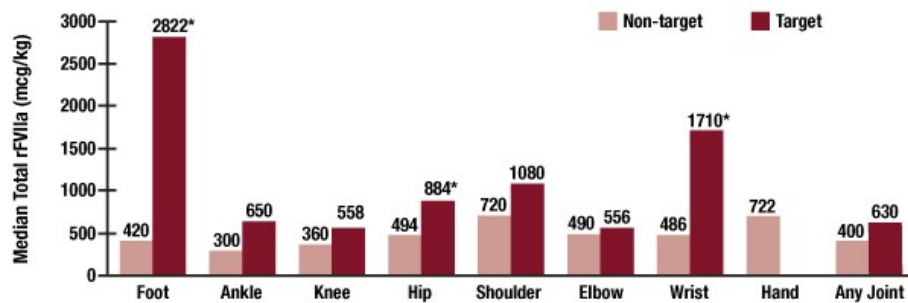


Figure 1

Exposure to rFVIIa by joint. Asterisk indicates that median values are based on <5 observations. From Valentino LA, et al, for the HTRS Investigators. Poster presented at: 22nd Congress of the International Society on Thrombosis and Haemostasis; July 11-16, 2009; Boston, MA.

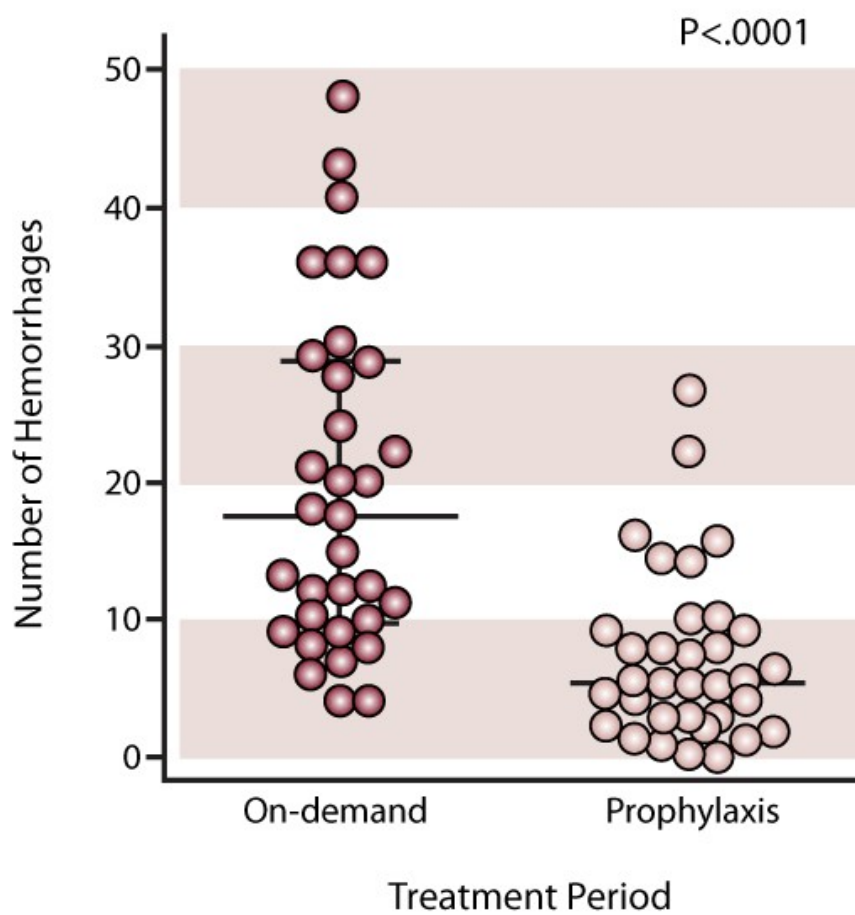
Study investigators examined 2041 rFVIIa-treated bleeds documented in the registry between 2004 and 2008 to identify hemarthroses and determine whether specific joints and target joints were more difficult to treat. Each bleed was analyzed for initial and subsequent dosing, from which the mean and total rFVIIa dose, number of doses, and treatment duration were calculated. It was determined, based on calculations, that load-bearing joints required lower doses than non-load-bearing joints, and total dosing varied by joint (see [Figure 1](#)) and was significantly greater for target joints. Overall, the effectiveness of rFVIIa (90%) was comparable between non-target and target joints, with no thrombotic events reported.

#### aPCC

In a meta-analysis of aPCC, Valentino reviewed 6 studies and 34 patients with hemophilia A or B with inhibitors to assess [The Benefits of aPCC Prophylaxis](#), specifically examining safety and efficacy. Thirty-one of 33 patients (94%) for whom bleeding data were available prior to prophylaxis experienced a decrease in rate of hemorrhage and had, on average, a 63.9% reduction in bleeding episodes during aPCC prophylaxis (see [Figure 2](#)).<sup>29</sup>

Moreover, in 3 studies that assessed all joint bleeding, 18 evaluated patients experienced an average reduction of approximately 75% while on prophylaxis regimens ([Figure 3](#)). No thrombotic or other complications were reported.

The meta-analysis suggests that aPCC administered prophylactically can be safe and effective for reducing bleeding events in inhibitor patients with hemophilia A.



**Figure 2**

Annual frequency of bleeding\* prior to prophylaxis (n=33) and during prophylaxis (n=34). Asterisk indicates that the type of hemorrhage measured differed among the studies. Each point represents the average annual bleeding frequency during the treatment period. The median and interquartile range are shown by the horizontal bars. From Valentino LA. Poster presented at: 22nd Congress of the International Society on Thrombosis and Haemostasis; July 11-16, 2009; Boston, MA.

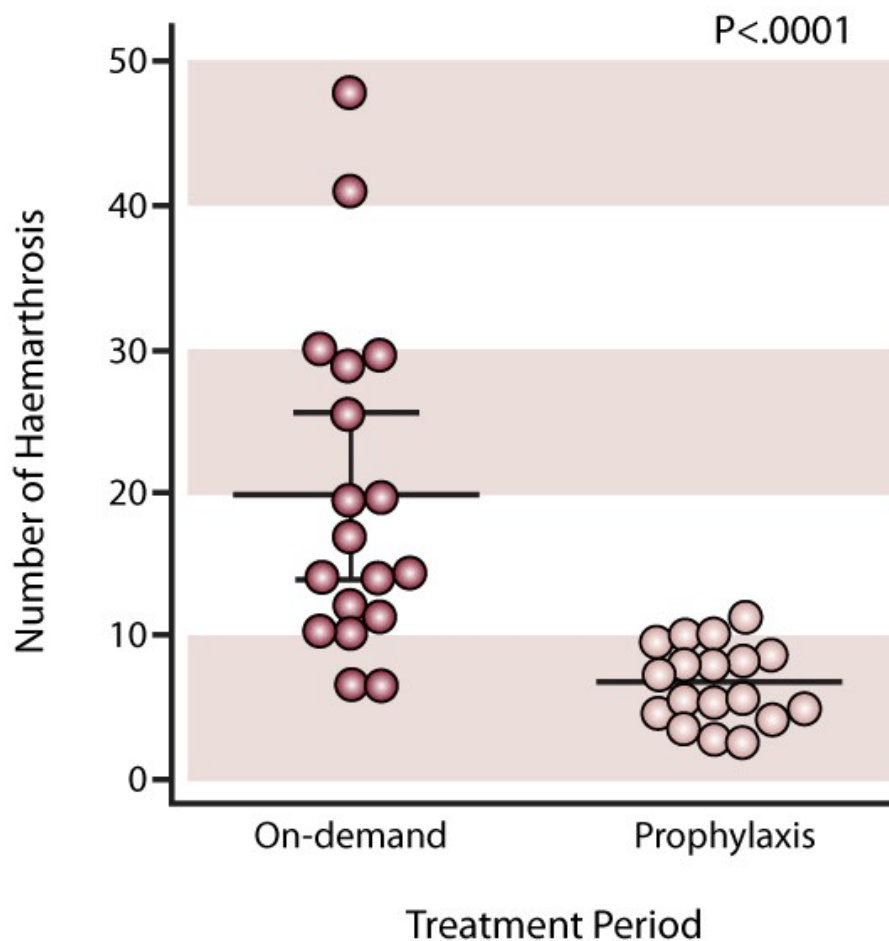


Figure 3

Annual frequency of joint bleeding\* prior to prophylaxis (n=18) and during prophylaxis (n=18). Asterisk indicates studies that measured joint hemorrhages. Each point represents the average annual bleeding frequency during the treatment period. The median and interquartile range are shown by the horizontal bars. From Valentino LA. Poster presented at: 22nd Congress of the International Society on Thrombosis and Haemostasis; July 11-16, 2009; Boston, MA.

#### Combination Bypassing Therapy

Klintman and investigators from the Malmö Centre for Thrombosis and Haemostasis in Sweden examined how use of saturating levels of FVIII in combination with either aPCC or rFVIIa affected thrombin generation in vitro: [aPCC in Combination With FVIII Potentiates In Vitro Thrombin Production in Inhibitor Plasma](#). Samples of platelet-poor plasma from the study population were spiked with either aPCC or rFVIIa and a FVIII product. Investigators found that even with no bypassing agent added, thrombin production increased with increased FVIII dose level. Several treatment strategies were simulated: aPCC with FVIII, rFVIIa with FVIII, and combination aPCC and rFVIIa with no FVIII. A potentiating effect was observed when aPCC was combined with one of the FVIII products, resulting in larger than expected thrombin generation; however, when rFVIIa was combined with FVIII, the effect was only additive. When aPCC and rFVIIa were combined without FVIII, an additive but not synergistic effect on thrombin generation was observed.<sup>21</sup>

#### Comparative Bypassing Therapy

Approximately 10% to 20% of bleeds in inhibitor patients cannot be controlled by initial use of aPCC or rFVIIa.<sup>16,22</sup> The sequential administration of both agents has been under investigation, as such a regimen is reported to have a positive synergistic effect.<sup>22</sup> Gringeri and colleagues analyzed the efficacy and safety of sequential combined bypassing therapy (SCBT), defined by the study team as administration of rFVIIa and aPCC within 12 hours of each other, in 2 children and 4 adults with

hemophilia A: [The Sequential Combined Bypassing Therapy Is Effective and Safe in the Treatment of Unresponsive Bleeds in Hemophilia Patients With Inhibitors](#). All subjects had high-responding inhibitors and were unresponsive to aPCC and rFVIIa alone. Sequential treatment was administered alternating one aPCC dose (range 50-80 U/kg) with one or two rFVIIa doses (range 90-270 µg/kg) every 4 to 12 hours. Complete bleeding control was achieved in 12 to 24 hours in all patients. SCBT was discontinued after 2 to 15 days and prophylaxis with aPCC or rFVIIa initiated thereafter in all patients. No adverse effects were noted, except for a rise in D-dimer levels in 3 of 6 patients. The study team concluded that SCBT may represent a valid salvage treatment for unresponsive bleeds, but larger clinical trials are warranted to confirm this finding.<sup>22</sup>

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## Hemophilia B

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Hemophilia B is a rarer disease (ie, one-fifth as common as hemophilia A), and little is known about the nature and treatment of this bleeding disorder. Even less is known about the diagnosis and management of FIX inhibitors.<sup>4</sup> National and international registries and other surveillance systems have emerged to play a useful role in the collection of data for the further study of hemophilia B, including epidemiology, natural history, patient- and treatment-related risk factors, and treatment strategies.

Pipe and investigators conducted an analysis of data captured from the HTRS Registry between 2004 and 2008 on [Use of Recombinant Factor VIIa \(rFVIIa\) in Individuals With Congenital Hemophilia B Complicated by Alloantibody Inhibitors to Factor IX](#). The study team examined rFVIIa from several parameters, including dosing, safety, and effectiveness. Bleeding episodes were recorded for patients with hemophilia A (377 patients) or B (36 patients) and inhibitors. rFVIIa was administered for 2041 bleeding episodes. Individual episodes were analyzed for mean and total rFVIIa dose, number of doses, and treatment duration.<sup>23</sup>

The study team found that bleeding was stopped (91.9%) or slowed (6.1%) in the hemophilia A cohort and stopped (84.6%) or slowed (13.1%) in the hemophilia B cohort ([Table 2](#)). Investigators concluded that, across most bleeding types, the total rFVIIa dosage, number of injections, and treatment duration were higher for hemophilia B patients with inhibitors than for hemophilia A patients with inhibitors.

Soucie and colleagues launched their own investigation of hemophilia B by conducting a pilot study on [Inhibitor Surveillance and Mutation Analysis](#) as part of the CDC-sponsored Universal Data Collection project.<sup>24</sup>

Since January 2006, 125 hemophilia B patients from 12 US HTC's have been enrolled. Mean follow-up time is 2 years. To date, the following observations have been reported:

- 52 distinct mutations
- Missense mutations, nonsense mutations, small insertions or deletions, one promoter mutation, and potential splice site changes noted in several patients
- History of inhibitors reported in 2 patients with severe disease
- No new inhibitors detected during 257 person-years of follow-up

Before inhibitor rates and the influence of specific mutations can be assessed accurately, more patients and longer follow-up are needed.

**Table 2. Effectiveness of rFVIIa**

	rFVIIa Treatment Outcome, N (%)	
	HemAwl	HemBwl
<b>Total Bleeding Episodes</b>	<b>1645</b>	<b>396</b>
<b>Stopped</b>	<b>1511 (91.9)</b>	<b>335 (84.6)</b>
<b>Stopped, but rebled within 48 hrs</b>	<b>11 (0.7)</b>	<b>1 (0.3)</b>
<b>Slowed</b>	<b>100 (6.1)</b>	<b>52 (13.1)</b>
<b>No improvement</b>	<b>23 (1.4)</b>	<b>8 (2.0)</b>
<b>Single-dose Treated Episodes</b>	<b>505</b>	<b>44</b>
<b>Stopped</b>	<b>488 (96.6)</b>	<b>44 (100.0)</b>
<b>Stopped, but rebled within 48 hrs</b>	<b>1 (0.2)</b>	<b>0</b>
<b>Slowed</b>	<b>12 (2.4)</b>	<b>0</b>
<b>No improvement</b>	<b>4 (0.8)</b>	<b>0</b>

From Pipe SW, et al, for the HTRS Investigators. Poster presented at: 22nd Congress of the International Society on Thrombosis and Haemostasis; July 11-16, 2009; Boston, MA.

## Conclusion

Although hemophilia continues to be associated with significant morbidity in patients with inhibitors, research efforts have led to improved quality of life for all patients with the bleeding disorder. As research continues to move forward, particularly in areas concerning patient- and treatment-related risk factors, immunogenetics, and treatment strategies, such endeavors likely will yield the requisite knowledge to treat the disorder more effectively or prevent it entirely.

The 2011 HTC CME NetWorkShops™ promise to be exciting and insightful, with a new array of posters and an impressive roster of presenting faculty. Please indicate your level of interest in attending or hosting an upcoming HTC CME NetWorkShop™.

- Very interested
- Somewhat interested
- Not at all interested

Please log in to participate in this poll.

[View Results](#)

What topics do you believe should be addressed in the 2011 series of NetWorkShops™?

- Inhibitors
- Treatments
- Dosing strategies
- QoL issues
- Other (please specify)

Please log in to participate in this poll.

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