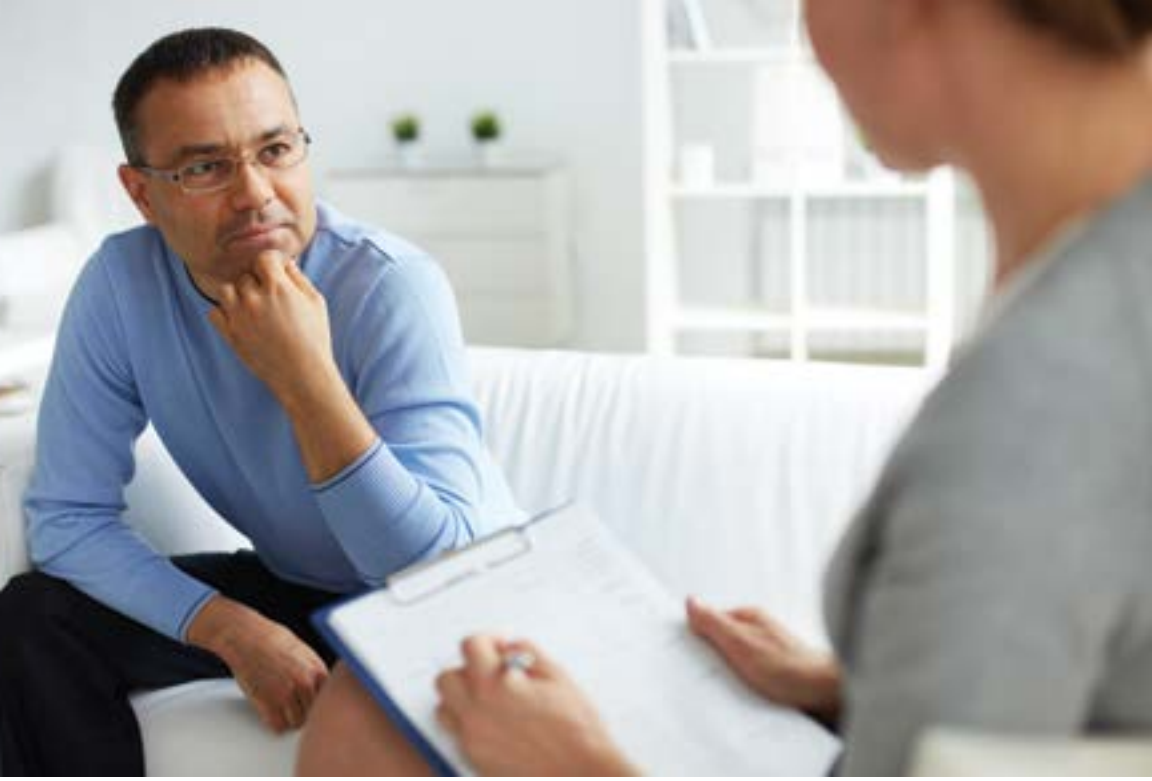
Living with an Inhibitor

Your guide to managing hemophilia with inhibitors

NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

HEMOPHILIA.ORG



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YOU'VE BEEN DIAGNOSED WITH AN INHIBITOR. NOW WHAT?

WHAT IS AN INHIBITOR?

When the body detects bacteria, viruses, and other foreign substances that can cause illness or harm, it creates **antibodies** to fight them. Sometimes, however, the immune system builds antibodies to attack things that were meant to help the body, such as certain medications.

An inhibitor is a type of antibody that attacks the infused **clotting factor** and stops the clotting factor product from working. This makes it more difficult to treat bleeds and to prevent bleeds from happening.

Inhibitors can develop in people with Hemophilia A (factor VIII (8) deficiency) and Hemophilia B (factor IX (9) deficiency) of all disease severities and ages, as well as von Willebrand disease (VWD) type 3 who infuse with clotting factor products. Inhibitors are most common in patients with Hemophilia A. It is important to know that when patients with Hemophilia B develop an inhibitor, they can develop allergic reactions to their clotting factor IX (9) product during or shortly after an infusion. These reactions can be severe, so it is important to discuss this with your hemophilia treatment center.

The way inhibitors are managed varies from person to person. No two people or situations are the same. The approach depends on things such as how high the inhibitor level (known as a **titer**) is at diagnosis and how the person responds to treatment.

In general, there are three goals for someone with an inhibitor:

- **GOAL ONE:** Prevent and treat bleeds
- **GOAL TWO:** Permanently remove the inhibitor
- **GOAL THREE:** Overcome the challenges of inhibitors in your daily life

Inhibitors can cause a number of concerns for patients with hemophilia and type 3 VWD and their families and caregivers. There is a risk of life and limb threatening bleeds and of long-term joint damage, as well as social, emotional, and financial strain. More is being learned about inhibitors all the time. There are now more treatment options than ever before to prevent and treat bleeds for patients with inhibitors. New treatments are being developed to help people live as healthy lives as possible.

THIS BROCHURE WILL HELP YOU LEARN:

- How to prevent and treat bleeds when you have an inhibitor
- How your healthcare providers may work toward removing inhibitors from your body
- Ways in which inhibitors can affect your lifestyle
- Tips for how to handle the cost of treatment
- The social and emotional impact of inhibitors

TIP FOR USING THIS BROCHURE
Not sure what some of the terms mean? Words in **orange** are explained in more detail in the Glossary at the back.

NEED MORE INFORMATION ON THE BASICS OF WHAT INHIBITORS ARE?
Check out NHF's companion brochure called "Facts About Inhibitors."

Clinical research about inhibitors is ongoing, so you can stay up to date on the latest prevention and treatment options by visiting **www.hemophilia.org/bleeding-disorders-a-z/overview/inhibitors**.

NHF recommends that you consult your hematologist or hemophilia treatment center before pursuing any course of treatment.

GOAL ONE: PREVENT AND TREAT BLEEDS.

An important part of managing hemophilia is preventing or reducing the frequency of bleeding episodes. **Prophylaxis** is the standard of care for preventing bleeds in many people with hemophilia and the benefits of prophylaxis can be important to individuals have an inhibitor. Prophylaxis involves regularly scheduled infusions of **clotting factor** or **subcutaneous** (under the skin) injections of a non-factor product (e.g., emicizumab, also known as Hemlibra®).

How you manage your hemophilia treatment depends on how much inhibitor you have: low or high level (titer). Inhibitors are measured using a blood draw and a laboratory test. The type of test determines how it is measured and which units are used to describe it, which can be Bethesda units (BU), Nijmegen Bethesda units (NBU), or chromogenic Bethesda units (CBU). The amount of inhibitor, which is called your titer, depends on the number of units measured in your blood.

- If you have ever had more than 5 Bethesda units, you have a **high-titer inhibitor.**
- If you have always had less than 5 Bethesda units, you have a **low-titer inhibitor**.

THERE ARE THREE MAIN WAYS TO TREAT AND PREVENT BLEEDS FOR PEOPLE WITH INHIBITORS:

- High dose clotting factor*
- Bypassing agents*
- Non-factor therapies

**These therapies can also be used to treat bleeds*

HIGH DOSE CLOTTING FACTOR PROPHYLAXIS

For people with **low-titer inhibitors**, using more frequent and/or higher doses of infused clotting factor replacement products may be able to prevent bleeds and can often treat bleeds. However, for others with **high-titer inhibitor,** preventing and treating bleeds is more difficult. Even the highest doses of clotting factor replacement may not be enough to overcome the inhibitor and prevent or treat bleeds. Individuals with a high-titer inhibitor must be treated with **bypassing agents**.

BYPASSING AGENTS

Bypassing agents are treatment products may be used by people with low-titer and high-titer inhibitors. Bypassing agent products have other clotting factors that can form a clot by "bypassing," or going around, the body's need for factor VIII (8) or factor IX (9).

THERE ARE TWO MAIN TYPES OF BYPASSING AGENTS:

1. Activated prothrombin complex concentrate, or aPCC (e.g. Feiba®), which are used to prevent and treat bleeds
2. Recombinant activated factor VIIa (7a) concentrate (e.g. SevenFact®, Novoseven®), which are used to treat bleeds

See NHF's Medical and Scientific Advisory Council (MASAC) treatment recommendations at www.hemophilia.org/ProductInfo for the names and characteristics of these bypassing agents.

WHAT ELSE IS IMPORTANT TO KNOW ABOUT BYPASSING AGENTS?

Bypassing agents can be very effective. They also do have some drawbacks. The first is that it hard to judge how well a medication is working. Different patients respond differently to the two types of bypassing agents and there is no standard lab test to determine how well a bypassing agent is working to prevent a bleeding episode. You may not know that it is not working as well as it could until you have a bleeding episode. There can be some trial and error in finding the right treatment and right dosing, which may be costly and time consuming. Occasionally, aPCCs may cause the inhibitor titer to rise because they contain factor IX (9) and small amounts of factor VIII (8). The HTC physician should perform frequent inhibitor tests to be sure this is not happening.

IF THE INITIAL DOSE OR TYPE OF MEDICATION IS NOT WORKING TO PREVENT BLEEDS, YOUR DOCTOR CAN DO ONE OR MORE OF THE FOLLOWING:

- Adjust the dose of the bypassing agent up or down
- Change the type of bypassing agent
- Change how often the bypassing agent is given
- Add additional medications

Another challenge is that having to infuse more often, or having infusions that take a longer time to fully inject, may contribute to difficulty accessing veins. Recombinant factor VIIa (7a) requires frequent infusions. aPCCs require the product to be infused very slowly, resulting in long infusions, to avoid potential reactions that may result from infusing too quickly.

Because patients with hemophilia are not deficient in the proteins in bypassing products, they should be given under close supervision because of potential for a **thrombosis** (a blood clot). A blood clot can occur anywhere in the body. This treatment complication is rare, but it can be serious, leading to a heart attack, stroke, or death. There are several reasons why a person may develop a blood clot after infusing with a bypassing product. The dosage of bypassing agent may be too high, or it is being infused too frequently. Clots can also form if the person is using both a bypassing agent and oral medications such as aminocaproic acid (e.g. Amicar®) or tranexamic acid (e.g. Lysteda®). These two types of medications prevent clots from breaking down and should not be used at the same time as a bypassing agent. Do not treat bleeds with an aPCC bypassing agent if you are using emicizumab (Hemlibra®) prophylactically, as doing so increases the likelihood you will develop a blood clot.

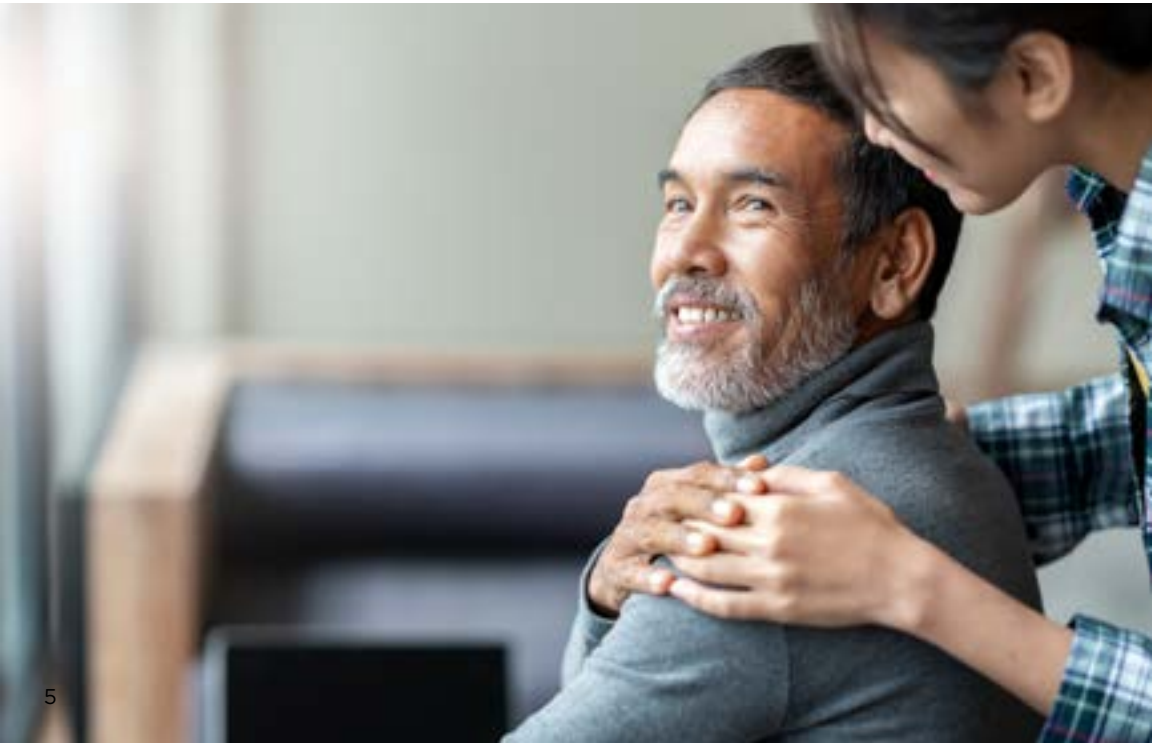
Finally, the treatment cost for bypassing products is significantly higher than for clotting factor. Cost can be a barrier to using bypassing agents (see section below on financial and insurance issues)

NON-FACTOR PRODUCTS:
New therapies that work in different ways in the body than clotting factor replacement or bypassing agents, to help prevent bleeding were first approved by the FDA in 2018. While traditional therapies were delivered by infusion into a vein, many of these new therapies require only an injection just under the skin (subcutaneous).

Emicizumab (Hemlibra®) is a non-factor treatment option that mimics clotting factor and is available for patients with hemophilia A (factor VIII (8)) with and without inhibitors, to prevent bleeding episodes. This product is a laboratory-engineered protein given by an injection under the skin that works by replacing the function of factor VIII (8) in clotting. Since it is not actually factor VIII (8), the inhibitor does not work against it. After the first series of weekly doses for four weeks, dosing may be weekly, every two weeks, or every four weeks.

Emicizumab (Hemlibra®) cannot be used to treat bleeds. If the individual has a bleeding episode, they will need to treat the bleed with standard clotting factor or a bypassing agent. Also, this product does not treat the inhibitor or get rid of it. The inhibitor titer might decrease significantly while on the non-factor product, however, if clotting factor is used to treat a bleed, the inhibitor titer will increase again.

There are other types of new therapies in different stages of research, so additional treatment products may become available. Some of these treatments are being researched for those with hemophilia A or B, with or without an inhibitor. For more details and the most up to date information on future therapies, please visit ***https://www.hemophilia.org/bleeding-disorders-a-z/treatment/future-therapies.***



WHAT ELSE IS IMPORTANT TO KNOW ABOUT NON-FACTOR PRODUCTS?
Non-factor products may affect some laboratory blood tests, including tests to measure factor activity levels and inhibitor titers. Although some non-factor treatments replace the role of factor in clotting, they work differently in the body than factor. This difference may cause tests to give misleading results. If standard tests to check factor levels are ordered in an emergency room or before surgery, they may indicate the individual taking emicizumab (Hemlibra®) has normal levels and does not have hemophilia or need treatment, even if the levels are very low. Individuals taking emicizumab (Hemlibra®) who are tested for an inhibitor with a Bethesda or Nijmegen-Bethesda assay will get a negative result, indicating that they do not have an inhibitor, even if they have a high titer inhibitor. ***Individuals taking emicizumab (Hemlibra®) must be tested with a Chromogenic assay to get a real inhibitor result.***

Communicate with your healthcare providers when you are treating with non-factor products to avoid any errors, prior to blood tests or medical procedures. Finally, individuals using emicizumab (Hemlibra®) should only treat with the aPCC bypassing agent under close supervision of a healthcare provider because they could develop a blood clot with higher doses for more than one day.

If interested in learning more about research developments and new treatments, please contact your Hematologist. Please visit hemophilia.org and look for the Future Therapies section for more updates, information, and answers to frequently asked questions.

GOAL TWO: PERMANENTLY REMOVE THE INHIBITOR.

Prevention and treatment of bleeding episodes is only part of treating people with inhibitors. Next, we look at ways to get rid of inhibitors themselves.

Immune tolerance induction

For some people, the best option to try to rid the body of inhibitors is **immune tolerance induction**, or ITI. The goal of ITI is to "teach" the body to accept the **clotting factor**. Another way to think about ITI is that it helps the body not see the factor as a threat. When ITI is successful, the body "remembers" that the factor treatment is not a foreign object and belongs there, and the inhibitor will slowly disappear.

ITI is done by giving individuals with an inhibitor more frequent infusions and/or higher doses of clotting factor over a given time period. It can take weeks or months, and in some cases years until the body gets used to the factor. There are many different protocols for ITI that your provider might use, which means that not all individuals will have the same treatment plan. For many individuals, especially young children, **a port** (a surgically inserted device to help give clotting factor through a vein) may be needed if it is difficult to find a vein to infuse. **Ports** can make an individual more likely to develop an infection, so it is important to talk to your doctor before one is inserted. It is also important to discuss with your doctor about how ITI will be given to you or your child. Write down any questions you may have and bring them to your doctor's appointment.

How well does ITI work?

ITI can work very well, even though it can be a long process. In fact, ITI can remove inhibitors in about 70% of people with hemophilia A and 30% of those with hemophilia B. For others, ITI can decrease their bleeding complications. ITI is most successful if it is started when the individual's inhibitor titer is less than 10.0 units but there may be some value in starting earlier regardless of titer. Talk with your healthcare provider.

WHEN DETERMINING WHETHER ITI IS SUCCESSFUL, THREE FACTORS ARE CONSIDERED:

1. The inhibitor titer is reduced to a negative value after being given a dose of clotting factor, a result typically less than 0.5 units
2. After getting a dose of factor, the factor level measured should be at least 66% of what the factor level was expected to be.
3. The half-life of clotting factor given to the patient is at least 6 hours.

Which products are used for ITI?

Many individuals start ITI using the same clotting factor product that they were using when they developed the inhibitor. Some individuals may switch to a different factor product, if their previous product no longer works. Your doctor will discuss the appropriate products with you and make a recommendation. Remember, everyone is different. What works for one person may not work for another.

Things to consider if you are thinking about ITI

Be sure to talk to your doctor about the benefits and risks of ITI. If you already go to a hemophilia treatment center (HTC), you may find support and information from the staff. There are several things to keep in mind.

ITI requires a lot of time for clinic visits and treatments. It can disrupt your normal routine and that of your family or caregivers. And depending on your progress, the treatment schedule may vary or change from time to time. ITI can also be costly and the duration of ITI treatment can range from months to years. To get through these challenges, you and your family, or others providing you support, will need commitment, dedication, and patience. Those who use a non-factor therapy, like emicizumab (Hemlibra®) for preventing bleeds should also talk to their doctor about any considerations for doing ITI.

THE GOOD NEWS IS THAT HELP IS AVAILABLE IF YOU KNOW WHERE TO LOOK FOR IT.

Some people rely on their family for support. Others find help through counseling at an HTC. Many people find that both are necessary to go through ITI successfully.

GOAL THREE: OVERCOMING THE CHALLENGES OF INHIBITORS IN YOUR DAILY LIFE.

People with inhibitors can live long, fulfilling lives. However, people with inhibitors and their families often face challenges, such as those discussed in this section. Finding support and resources to help you and your family through such challenges is key.

Joint and physical activity concerns
Bleeds happen in people with hemophilia who have and don't have inhibitors. For people with inhibitors, bleeds are harder to control and take longer to heal.
Below are some of the ways you can deal with these types of bleeds:

Being physically active is important to strengthen your joints and muscles which helps to prevent joint and muscle bleeds and promote good health. Typically, lower-risk activities are advised. But first speak to your healthcare provider, especially your physical therapist, about whether that physical activity would be good for you.

Treating bleeds may take longer when you have an inhibitor, so more damage may be done to joints and muscles. You may need to use protective gear and/or assistive equipment. These may include crutches, a wheelchair, walker, sling and splints.

Complete recovery from a joint or muscle bleed is important to reduce your chances of having a repeat bleed in the same joint or muscle soon after. Working with a physical therapist will help you recover from such a bleed.

People with inhibitors may experience joint damage from repeated bleeds in the same joint, known as a target joint, over time. Joint damage can be treated by surgical and nonsurgical methods.

Financial and insurance coverage considerations
Treatment for hemophilia is costly, even for people without inhibitors. Once an inhibitor develops, treatment can become very expensive. It is important to remember that insurance companies do not always cover all treatment costs. Because of this, patients and their families must consider both the initial costs of treatment and the projected costs of the entire therapy.

People going through inhibitor treatment should be aware that some costs get paid "out of pocket." And many insurance plans have a limit to how much they will pay for treatment. If you go to an HTC, be sure to talk to a social worker and/or hospital insurance verifier. They can help you work through some of the items listed below. In addition, you can go to hemophilia.org and search for the Personal Health Insurance Toolkit to help assess what your insurance plan will cover.

Things to consider about the cost of coverage of treatment

1. Does your doctor need to provide extra reasons to justify your treatment?
2. Does your insurance plan have a special case manager for people with hemophilia?
3. Are there costs your insurance will not cover?
4. Are there programs from the government or drug companies that can help lower your costs?
5. Will you be treated in a hospital or in an outside office or clinic?

Impact of inhibitor treatment
Some treatment plans for inhibitors are intense and long lasting, which can be hard on the whole family. It can cause emotional stress and affect your social life, work and school.
Some of the ways you may be affected include:

- You may have to travel to your hemophilia provider more often to get the care you need.
- Some treatments require increased number of infusions and patients may develop a fear of needles.
- More frequent infusions sometime require use of a **port** (a surgically inserted device to help give factor through a vein) and infections can occur with the port.
- Treatment may cause you or your caregivers to miss work or school.

Social issues for children at school
Treatment can be especially hard on children and teens.
They may experience some of the following:

- Limited activities to prevent bleeds or if doing ITI due to intensive therapy
- Social issues from the burden of ongoing treatment
- Greater anxiety or depressed moods due to limited physical activity
- Challenges at school from absences due to increased treatment

That's why support is so important for children. Family members, caregivers, doctors, and other health experts can help. Staff at an HTC can help parents with their children's physical and emotional changes. They can suggest safe activities that meet the needs of each child.

Children may require accommodations, modifications and support at school. You can get help completing paperwork, such as developing a **504 Accommodation Plan** or an **Individualized Education Plan (IEP)**.

SOCIAL WORKERS CAN PROVIDE HELP or refer family members to therapists or counselors who can help you with the impact of inhibitors on you, your child, and the rest of the family.

Challenges at work

Whether you have an inhibitor yourself or are a caregiver for a child with an inhibitor, the frequent treatment and medical visits can pose challenges at work. The Americans with Disabilities Act (ADA) and Family Medical Leave Act (FMLA) offer protections that may be relevant for you. For instance, they can help you request reasonable accommodations or time off for treatment for you or your child.

What you choose to disclose about your bleeding disorder or your child's in the workplace is an individual decision. You can find more resources and support from your local NHF chapter, HTC or online at: **http://stepsforliving.hemophilia.org/step-out/workplace-issues**

Inhibitors and family dynamics

When someone has an inhibitor, it can take a toll on the whole family. Challenges can arise when more time or attention is given to a child or partner with a bleeding disorder. Other issues may surface when asking extended family for support or when educating them on how inhibitors can affect everyone's lives.

Managing these dynamics can lead to added stress. The social workers at your HTC and local NHF chapters have resources to help navigate these relationships.

INHIBITOR RESEARCH

DOCTORS AND OTHER HEALTH EXPERTS ARE LEARNING MORE ABOUT HEMOPHILIA AND INHIBITORS ALL THE TIME.

The treatment landscape for people with inhibitors is evolving. There has been a growing interest in new types of treatments, including non-factor and gene therapies which are in different stages of development. The results appear promising. New and future treatments may be able to reduce the treatment burden for people with and without inhibitors.

For the most up-to-date treatment options visit hemophilia.org and look for the MASAC Recommendations Concerning Products Licensed for the Treatment of Hemophilia and Other Bleeding Disorders.

GLOSSARY

504 Accommodation Plan is a legal document listing specific accommodations for students with a disability, such as extra time to complete assignments when absent.

Anaphylaxis is a severe allergic reaction.

Antibodies protect the body from bacteria, viruses and other invaders. They are formed by the immune system in response to a foreign substance that enters the body.

Titer is the level or amount of inhibitor in the patient's blood, measured in Bethesda units (BU), Nijmegen Bethesda units (NBU), or chromogenic Bethesda units (CBU).

Bypassing agents are clotting factors (other than factor VIII (8) or factor IX (9) used to treat people who have inhibitors. They can form a clot to stop bleeds by "bypassing " the need for the deficient clotting factor (VIII or IX).

Clotting factor (often called factor) a treatment product that is infused and replaces the missing clotting factor VIII (8) for people with Hemophilia A or missing clotting factor IX (9) or people with Hemophilia B, so that the blood can clot properly.

High-titer inhibitor means your body has a strong response against the clotting factor. Your test results at any point have been more than 5 units.

Immune tolerance induction (ITI) is a type of treatment to eliminate the inhibitors from an individual's body and they stop creating them.

Individual Education Plan (IEP) is a plan created to ensure that a child who has a disability identified under the law and is attending an elementary or secondary educational institution receives specialized instruction and related services, including necessary modifications.

Low-titer inhibitor means your body has a low response against the clotting factor. Your test results have always been less than 5 units.

Port(s) are devices that are surgically placed in the body to make it easier to administer clotting factor products into the bloodstream. Some of them are inserted under the skin in the chest. Your doctor will help you decide which type is best for you or your child.

Prophylaxis is the administration of clotting factor on a regular schedule to prevent bleeding.

Thrombin is an enzyme that converts fibrinogen into fibrin to strengthen a clot.

Thrombosis is a clot that forms in an artery or vein in the body. It may occur spontaneously or following treatment with aPCCs.

NOTES/QUESTIONS FOR YOUR HEALTHCARE PROVIDER:

WANT TO KNOW MORE ABOUT LIVING WITH INHIBITORS?

The National Hemophilia Foundation is your source for information on all bleeding disorders. On our website, hemophilia.org, you can:

- Find a hemophilia treatment center (HTC) or NHF chapter near you
- Get information on our online and in-person inhibitor education programs
- Learn what the latest recommendations are for treatment
- Access tools to advocate for healthcare coverage

At **stepsforliving.hemophilia.org**, you can also find interactive information, videos and tools for living with a bleeding disorder, including an inhibitor, at any life stage.

YOU ARE NOT ALONE

The community of healthcare professionals and people with bleeding disorders can help you. Families, friends and loved ones often come together in groups to support each other. During NHF's Bleeding Disorders Conference, people who have (or had) inhibitors and their caregivers can meet. Many form strong bonds that last a lifetime.

Connect with other families affected by bleeding disorders in your area

Visit https://www.hemophilia.org/Community-Resources/Chapter-Directory

Learn more about NHF's Inhibitor Education

Visit https://www.hemophilia.org/educational-programs/education/inhibitor-education

For more information, contact NHF's Information Resource Center at

800.424.2634 or handi@hemophilia.org

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The National Hemophilia Foundation (NHF) is dedicated to finding better treatments and cures for inheritable bleeding disorders and to preventing the complications of these disorders through education, advocacy and research. Established in 1948, the National Hemophilia Foundation has chapters throughout the country. Its programs and initiatives are made possible through the generosity of individuals, corporations and foundations as well as through a cooperative agreement with the Centers for Disease Control and Prevention (CDC).