NHF News Briefs

January 12 – January 18, 2018

This report includes selected news items from the past week on issues of concern to the bleeding disorders community. It is designed to help keep NHF national and local leadership and staff informed of the latest information from the news media. It will be distributed by email on Thursday of each week, covering important news items from the previous seven days. Subjects covered will include hemophilia, other bleeding disorders, gene therapy, hepatitis, HIV/AIDS, and others.

January 9, 2018
Warwickonline.com

10-Year-Old Madeline Loves to Lend a Hand

By Ethan Hartley

Anybody who believes one person can't make a difference in the world – or that only adults can orchestrate change in life – should have a sit-down with 10-year-old Madeline Murray.

The 4th-grader at Hoxsie Elementary School in Warwick would be happy to schedule a time, provided she doesn't have to miss school in order to do so – she likes school.

She also likes helping people, and has already spent more than two years of her short life raising money through selling arts and crafts projects and colorful drawings to benefit a variety of causes and organizations in Rhode Island.

"I thought what if I made my own business to help people?" pondered Madeline in recollection. And thus, in June of 2017, Madeline's Helping Hands was born.

Madeline and her brother T.J., 7, get requests for drawings from Facebook or through the mail and then they send out their creative creations for $1 or $2, and always accept additional money if offered. So far they have been able to purchase 2,000 stickers and 540 non-latex bandages for Hasbro Hospital's Tomorrow Fund, as well as dolls and stuffed animals for Alzheimer's patients at a Rhode Island care facility.

Madeline, T.J. and their mother Meagan were also invited on a trip to D.C. in March with Senators Sheldon Whitehouse and Jack Reed to participate as advocates against the repealing of the Affordable Care Act. The visit came during a month dedicated to raising awareness about bleeding disorders – as T.J. suffers from a rare blood clotting disorder called Von Willie Brand's disease.

The most recent endeavor for Madeline's nonprofit – and her mother will be the first to tell you, Madeline truly does run the ship – was to raise $150 for the New England Hemophilia Association (NEHA) in order to send a family to their annual camping excursion along the banks of Lake Winnipesaukee.

To help with the mission the Murrays reached out to the Providence Bruins, who worked with Madeline to have a ticket drive for their Tomorrow Fund night, which benefits Hasbro Hospital's Tomorrow Fund, where $3 of every ticket purchase would go towards her donation goal. She raised $250 from the drive, and a private company has since anonymously agreed to match that donation and double it to $500.

"It's a huge deal," Meagan said of her daughter's initiative to send a family to the camp. "These are kids like him [T.J.] who might not always get along because they can't play the contact sports or do a lot of the activities other kids can do – or they can but they're very limited. Bleeding disorders are pretty rare, so they get to be around others who know what they're going through."

While the camp gives kids the opportunity to engage in a normal camp experience with other kids battling the same afflictions, it gives the rest of their family the opportunity to engage with other

parents and learn information on the disorders through educational seminars. According to the NEHA website, attendance at the camp has increased by 93 percent since 2014, and now serves 75 families (300 individuals) from all New England states and New York.

The cost incurred by a family to go to camp is around $125 – hence Madeline's goal of $150, which takes into consideration the gas money needed to drive to New Hampshire for the retreat. However since she exceeded her goal by so much, what does she plan on doing with the remainder of the money?

"NEHA has to pay a lot of money to run the camp, so I was thinking what if the rest of money – after we send one family to the camp – could go to NEHA so they can work on the camp," she suggested, saying that they could use the money to improve their campsite playground as an example.

Madeline points to a moment when she was half as old as she currently is as the moment she realized she wanted to dedicate time and resources to helping others.

"When I was five, we were driving home and saw a lady on the ground. She wiped out on her motorcycle. My mom stopped the car, told us to stay put, got out and helped clean up the lady," she said. "When she was all set, my mom helped pick up the bike. When she got back in our car I asked if she knew the lady. My mom said no, but that it was the right thing to do. I have never forgotten that."

Meagan said that the trip to D.C. is what really pushed and inspired Madeline to take her giving endeavors more seriously and turn Madeline's Helping Hands into a legitimate nonprofit. She said that Madeline got very passionate during the meeting with the senators, pounding her fists on the table and decrying the notion of cutting healthcare benefits.

"When we came back she was like, 'What else can I do to help?' She's probably one of the most caring people you'll meet. She just wants to help," Meagan said. "I'm so proud of her. I'm very inspired by and proud of my kids."

Madeline isn't done either. She's already planning on talking to Hasbro staff when she goes this month to donate the stickers and asking if she can raise money to purchase toys or coloring books for the patients there.

"It just goes to show it's something anyone can do," said Dave Denitto, vice president of tickets and events for the Providence Bruins. "Whether you're 10 years old or 30 years old, anyone can help."

To view more of Madeline's work, visit her Facebook page at Facebook.com/Madelineshelpinghands/. To reach out to the Providence Bruins for a fundraising endeavor, contact Dave Denitto at 680-4706.

January 15, 2018
Juneauempire.com

A Gamer's Wish Granted

By Kevin Gullufsen

Local boy Graysen Fawcett is a pretty typical first grader. He's a "rough and tumble" kid with a lot of energy, according to his mother. He likes video games like Minecraft and Super Mario. He's got an older sister, Arianna, who looks out for him.

One of the things that makes this 6-year-old unique, though, is the very same thing that got him a total room makeover this weekend: Graysen has hemophilia. Nominated by a nurse, Graysen was the recipient of a Make-a-Wish Foundation wish fulfillment that brought him a new TV, several video game systems and a video game library.

Volunteers, friends and family gathered to celebrate the reveal of his wish Saturday at the Juneau Gymnastics Academy in the valley.

The group had spent the morning setting Graysen's room up while his mother, Marion Fawcett, distracted Graysen and his friends with a trip to MacDonalds. When the room was finally ready, they showed him pictures of the results at a party at the gym, complete with a Super Mario cake.

Graysen couldn't wait to get home and try out the new Playstation 4, Nintendo Wii U and the virtual reality headset he received.

"I did not know it was going to get that much decorated!" Graysen said of his room.

What's first thing he's going to do when he gets home?

"I'm gonna play video games all night!" he said.

The volunteer effort to bring Graysen a little joy took about a year and a half. Three Juneau women, Kelsea Goodell, Erann Kalwara and Lisa Mielke, made it happen.

The Anchorage Make-a-Wish Foundation office assigned the trio to the job. It was the first wish the three women had worked on for a Juneau local.

They were all surprised by the generosity of local businesses. They don't remember getting any requests for donations turned down.

The reveal was "like Christmas" Goodell said.

"We've been excited for months. My heart was beating this morning. I was up at 8 and that doesn't happen," she said.

"We've all just been vibrating," Mielke said.

Hemophilia is a genetic disorder decreasing the ability of blood cells to clot. So if Graysen gets even a small cut, he could keep bleeding. He's got only about 5 percent of the normal amount of factor VIII protein, a component of blood which acts as a glue for platelets which form fibrous plugs when blood exits a blood vessel.

The disorder occurs in about one in 5,000 live births in the U.S. About 20,000 people in the country have hemophilia, according to the National Hemophilia Foundation.

A fever that might mean a day out of school for some kids would land Graysen in the hospital. Fevers can indicate a blood infection, which could be life-threatening for somebody with hemophilia.

Graysen was in the hospital with a fever during Halloween last year. His dutiful sister Ariana, 8, kept him company.

"She's always been there for him, helping out and looking out for him," Marion said.

Doctors have known about the disorder since Graysen's birth.

Treatment was intensive to start. Marion would have to take Graysen to the hospital for infusions of a medication called Alphanate every other day. The treatments temporarily increase the amount of factor VIII proteins in his blood.

Graysen would get spontaneous bleeds in his legs when he was younger but medication lessened the symptoms. Eventually, Graysen's doctors trained Marion to do the infusions at home.

That was a nerve-wracking experience for Marion, but she eventually became comfortable treating Graysen herself.

"The first time I infused him I stayed up all night crying because I thought I might have introduced air into the system," she said. "Now it's just a part of life."

The Alaska office of the Make-a-Wish Foundation serves about 60 young people every year. That breaks down to about 30 Alaskan children and 30 children from around the country wishing to come to Alaska to fulfill their wish, communications director Hannah Moderow said.

It's a fulfilling job, Moderow added.

"We are that little spark of joy that kids need when they're sick. It's really cool to get to hear the community rally for one of these kiddos," Moderow said.

The foundation hasn't had a Juneau wish in several years. Moderow could recall bringing a child up sometime in the last few years for a Juneau fishing trip as part of a wish fulfillment.

Make-a-Wish has three full-time employees in the state. They grant wishes across the state and into rural Alaska and depend on local volunteers to make everything happen.

Moderow said it's a common misconception that Make-a-Wish only grants wishes for terminally ill children. They actually grant wishes to children with all sorts of illnesses, terminal or not.

“One of the things we care most about is highlighting the communities that make a wish happen, that’s one of the big things,” Moderow said. “We rely on the generosity of volunteers, people like Erann and others.”

Though Graysen’s room is now a gamer’s paradise, his life will continue as normal — only, now he can take that rough and tumble spirit to the virtual world.

“I don’t think he sees it as a challenge, it’s just life. It’s just part of our life,” Marion said.

January 15, 2018
Globenewswire.com

Shire Granted EU Marketing Authorization for ADYNOVI® [Antihemophilic Factor (Recombinant), PEGylated] **For Adults and Adolescents with Hemophilia A**

- ***Marketing Authorization will enable patient access to ADYNOVI throughout Europe***

Shire plc, the global biotechnology leader in rare diseases, announced today that the European Commission (EC) has granted Marketing Authorization for ADYNOVI [Antihemophilic Factor (Recombinant), PEGylated], an extended half-life recombinant factor VIII (rFVIII) treatment, for on-demand and prophylactic use in patients 12 years and older living with hemophilia A. ADYNOVI is modified to last longer in the blood and potentially require less frequent injections than unmodified Antihemophilic Factor when used to reduce the frequency of bleeding. It is built on ADVATE® [Antihemophilic Factor (Recombinant)], a treatment used by hemophilia A patients worldwide for almost 15 years. ADYNOVI's proprietary PEGylation technology, exclusively licensed from Nektar Therapeutics, extends the time between treatments and offers a twice-weekly dosing schedule.1

"The European approval of ADYNOVI is an important milestone in our continued commitment to provide new treatment options for patients living with hemophilia A," said Dr. Peter Foertig, MD, Global Head Hematology Medical Affairs, Shire. "We believe that the twice-weekly prophylactic dosing, as well as the on-demand control of bleeding, offered by ADYNOVI will bring us closer to our goal of improving and personalizing disease management for hemophilia A patients in Europe."

The Marketing Authorization is based on outcomes from three Phase 3 clinical trials of patients with hemophilia A. These include a prospective, global, multi-center, open label, non-randomized study of patients 12 to 65 years of age; a prospective, uncontrolled, open label, multi-center study of patients 12 years of age and younger; and a study of perioperative control of hemostasis with interim study results from 15 patients with severe hemophilia A undergoing surgical procedures.2,3,4

Hemophilia A, designated an orphan disease by the EC, is a rare bleeding disorder that causes longer-than-normal bleeding due to lack of proper clotting factor VIII (FVIII) in the blood.5,6 The severity of hemophilia A is determined by the amount of factor in the blood, with more severity associated with lower amounts of factor.7 More than half of patients with hemophilia A have the severe form of the condition.7 Today, hemophilia A affects approximately 150,000 across the globe.8 It primarily affects males, with an incidence of one in 5,000 male births.9 Of the worldwide hemophilia patient population, an estimated 75 percent lack adequate treatment or access to treatment altogether.9

With this approval, Shire is now authorized to market ADYNOVI in the 28 Member States of the European Union (EU), as well as in Iceland, Liechtenstein and Norway.

About ADYNOVI

ADYNOVI was first approved as ADYNOVATE® [Antihemophilic Factor (Recombinant), PEGylated] by the Food and Drug Administration (FDA) in the U.S. followed by approval in Japan, Canada, and Colombia, and is approved as ADYNOVI in Switzerland. ADYNOVATE most recently received approval in Japan for use in hemophilia A pediatric patients under 12 years of age and those undergoing surgery in November 2017.

ADYNOVI SAFETY INFORMATION FOR EUROPE

Please consult the ADYNOVI Summary of Product Characteristics (SmPC) before prescribing, particularly in relation to dosing and treatment monitoring.

Contraindications

Hypersensitivity to the active substance, to the parent molecule octocog alfa or to any of the excipients listed in the SmPC. Known allergic reaction to mouse or hamster protein.

Special warnings and precautions for use

The medicinal product contains traces of mouse and hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

The formation of neutralising antibodies (inhibitors) against factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay.

In general, all patients treated with coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed.

After reconstitution this medicinal product contains 0.45 mmol sodium (10 mg) per vial.

Adverse Reactions

Common (Greater-than or equal to 1/100 to <1/10) : Headache, Diarrhea, Nausea, Rash

Uncommon (Greater-than or equal to 1/1000 to <1/100) : Factor VIII inhibition in previously-treated patients (PTPs), Hypersensitivity, Flushing

For more information, please refer to the ADYNOVI Summary of Product Characteristics here.

ADVATE SAFETY INFORMATION FOR EUROPE

ADVATE is contraindicated in patients with known anaphylaxis to mouse or hamster protein or other constituents of the product.

Allergic-type hypersensitivity reactions, including anaphylaxis, are possible and have been reported with ADVATE. Symptoms have manifested as dizziness, paresthesia, rash, flushing, face swelling, urticaria, dyspnea, and pruritus. Discontinue use if hypersensitivity symptoms occur and administer appropriate emergency treatment.

Carefully monitor patients treated with factor VIII products for the development of FVIII inhibitors by appropriate clinical observations and laboratory tests. Inhibitors have been reported following administration of ADVATE predominantly in previously untreated patients (PUPs) and previously minimally treated patients (MTPs).

If expected plasma FVIII levels are not attained, or if bleeding is not controlled with an expected dose, perform an assay that measures FVIII inhibitor concentration.

The serious adverse reactions seen with ADVATE are hypersensitivity reactions and the development of high-titer inhibitors necessitating alternative treatments to FVIII.

The most common adverse reactions observed in clinical trials (frequency greater than or equal to 10 percent of subjects) were pyrexia, headache, cough, nasopharyngitis, vomiting, arthralgia, and limb injury.

About Shire

Shire is the global leader in serving patients with rare diseases. We strive to develop best-in-class therapies across a core of rare disease areas including hematology, immunology, genetic diseases, neuroscience, and internal medicine with growing therapeutic areas in ophthalmics and oncology. Our diversified capabilities enable us to reach patients in more than 100 countries who are struggling to live their lives to the fullest.

We feel a strong sense of urgency to address unmet medical needs and work tirelessly to improve people's lives with medicines that have a meaningful impact on patients and all who support them on their journey.

www.shire.com

Forward-Looking Statements

Statements included herein that are not historical facts, including without limitation statements concerning future strategy, plans, objectives, expectations and intentions, projected revenues, the anticipated timing of clinical trials and approvals for, and the commercial potential of, inline or pipeline products, are forward-looking statements. Such forward-looking statements involve a number of risks and uncertainties and are subject to change at any time. In the event such risks or uncertainties materialize, Shire's results could be materially adversely affected. The risks and uncertainties include, but are not limited to, the following:

- Shire's products may not be a commercial success;
- increased pricing pressures and limits on patient access as a result of governmental regulations and market developments may affect Shire's future revenues, financial condition and results of operations;
- Shire conducts its own manufacturing operations for certain of its products and is reliant on third party contract manufacturers to manufacture other products and to provide goods and services. Some of Shire's products or ingredients are only available from a single approved source for manufacture. Any disruption to the supply chain for any of Shire's products may result in Shire being unable to continue marketing or developing a product or may result in Shire being unable to do so on a commercially viable basis for some period of time;
- the manufacture of Shire's products is subject to extensive oversight by various regulatory agencies. Regulatory approvals or interventions associated with changes to manufacturing sites, ingredients or manufacturing processes could lead to, among other things, significant delays, an increase in operating costs, lost product sales, an interruption of research activities or the delay of new product launches;
- certain of Shire's therapies involve lengthy and complex processes, which may prevent Shire from timely responding to market forces and effectively managing its production capacity;
- Shire has a portfolio of products in various stages of research and development. The successful development of these products is highly uncertain and requires significant expenditures and time, and there is no guarantee that these products will receive regulatory approval;
- the actions of certain customers could affect Shire's ability to sell or market products profitably. Fluctuations in buying or distribution patterns by such customers can adversely affect Shire's revenues, financial conditions or results of operations;
- Shire's products and product candidates face substantial competition in the product markets in which it operates, including competition from generics;
- adverse outcomes in legal matters, tax audits and other disputes, including Shire's ability to enforce and defend patents and other intellectual property rights required for its business, could have a material adverse effect on the Company's revenues, financial condition or results of operations;
- inability to successfully compete for highly qualified personnel from other companies and organizations;
- failure to achieve the strategic objectives, including expected operating efficiencies, cost savings, revenue enhancements, synergies or other benefits at the time anticipated or at all with respect to Shire's acquisitions, including NPS Pharmaceuticals Inc., Dyax Corp. or Baxalta Incorporated may adversely affect Shire's financial condition and results of operations;
- Shire's growth strategy depends in part upon its ability to expand its product portfolio through external collaborations, which, if unsuccessful, may adversely affect the development and sale of its products;
- a slowdown of global economic growth, or economic instability of countries in which Shire does business, as well as changes in foreign currency exchange rates and interest rates, that adversely impact the availability and cost of credit and customer purchasing and payment patterns, including the collectability of customer accounts receivable;

- failure of a marketed product to work effectively or if such a product is the cause of adverse side effects could result in damage to Shire's reputation, the withdrawal of the product and legal action against Shire;
- investigations or enforcement action by regulatory authorities or law enforcement agencies relating to Shire's activities in the highly regulated markets in which it operates may result in significant legal costs and the payment of substantial compensation or fines;
- Shire is dependent on information technology and its systems and infrastructure face certain risks, including from service disruptions, the loss of sensitive or confidential information, cyber-attacks and other security breaches or data leakages that could have a material adverse effect on Shire's revenues, financial condition or results of operations;
- Shire incurred substantial additional indebtedness to finance the Baxalta acquisition, which has increased its borrowing costs and may decrease its business flexibility;
- Our ongoing strategic review of our Neuroscience franchise may distract management and employees and may not lead to improved operating performance or financial results; there can be no guarantee that, once completed, our strategic review will result in any additional strategic changes beyond those that have already been announced; and

a further list and description of risks, uncertainties and other matters can be found in Shire's most recent Annual Report on Form 10-K and in Shire's subsequent Quarterly Reports on Form 10-Q, in each case including those risks outlined in "ITEM 1A: Risk Factors", and in Shire's subsequent reports on Form 8-K and other Securities and Exchange Commission filings, all of which are available on Shire's website.

All forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by this cautionary statement. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof. Except to the extent otherwise required by applicable law, we do not undertake any obligation to update or revise forward-looking statements, whether as a result of new information, future events or otherwise.

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January 16, 2018
Aidsmap.com

Hepatitis C Treatment Highly Effective in Harder-To-Treat People with HIV Co-Infection, Spanish Real-Life Study Shows

By Michael Carter

Hepatitis C virus (HCV) treatment using direct-acting antivirals (DAAs) is highly effective and safe in harder-to-treat people with HIV co-infection, Spanish researchers report in AIDS. A sustained virological response (SVR), or cure, was observed in 93% of people and only 0.4% stopped treatment because of adverse events. The large proportion of people had advanced fibrosis or had taken a previous course of HCV therapy. Liver cirrhosis/liver stiffness were the only factors associated with treatment failure and use of ribavirin increased the risk of side-effects.

Nevertheless, 87.5% of people with cirrhosis achieved an SVR and no one with cirrhosis who completed a 24-week course of treatment and underwent follow-up testing failed to be cured of hepatitis C. The study findings are highly encouraging for people with co-infection with advanced liver disease – in the past considered harder to treat – the study investigators conclude.

"The present work considered a heterogeneous, unselected cohort of coinfected patients who were treated for their HCV infection under normal clinical practice conditions, and contrasts well with highly-selective randomized clinical trials which do not always equate well to real-life settings," write the investigators.

"The real-life results of studies performed in developed countries implementing all-oral DAA based regimens in cohorts principally including difficult-to-treat patients (HIV coinfected, cirrhotic, and/or with previous therapy failures), confirm these results."

Approximately a third of HIV-positive people in Spain have co-infection with HCV. Liver disease caused by HCV is a leading cause of serious illness and death in people with co-infection. In recent years, HCV therapy using all-oral DAA regimens has been developed. In clinical trials, these combinations have achieved SVR rates in excess of 90%. However, there is relatively little data about the efficacy and safety of DAA combinations in people with HIV/HCV co-infection with characteristics usually associated with poorer treatment outcomes, especially more advanced liver disease or therapeutic failure using older regimens.

Investigators in eastern Spain therefore analysed outcomes in 515 people with co-infection who started an all-oral DAA regimen in 2015. Retrospective data were obtained on the proportion of people attaining an SVR 12 weeks after completing a 12 or 24-week course of therapy, and also the proportion of people experiencing adverse events. The investigators also conducted a series of analyses to see if specific patient or treatment factors were associated with the success of therapy or a greater risk of side-effects.

A total of 13 treatment centres in the region close to Valencia participated in the study. The participants had a median age of 50 years and 78% were male. Most (84%) had injecting drug use as their most likely mode of HCV infection. The most common HCV genotype was 1a (47%), with 20% carrying genotype 4 and 14% genotype 1b and 13% genotype 3. Just over half (54%) had cirrhosis, which was diagnosed using elastography (FibroScan, an assessment of liver stiffness) in 95% of

people. Just under half (46%) had taken a previous unsuccessful course of HCV therapy based on pegylated interferon or first-generation DAAs.

As regards HIV infection, 95% of individuals were taking antiretroviral therapy (ART) and 90% had a viral load below 50 copies/ml. Median CD4 cell count was 585 cells/mm3. To avoid potential drug interactions, a third of participants modified their ART before staring DAA therapy. The new combinations were mostly based on an integrase inhibitor.

The most widely used DAA regimen was ledipasvir/sofosbuvir (57%). Just over a third of people (37%) were treated with a ribavirin-containing regimen and 7% took a 24-week course of therapy.

Overall, 93% of people had an SVR 12 weeks after the completion of therapy. There was little evidence that outcomes were influenced by baseline characteristics such as age and sex, HCV viral load or previous use of HCV therapy.

The only factors associated with reduced chances of attaining SVR were cirrhosis ($p = 0.001$) and liver stiffness above 21kPa ($p = 0.001$).

Only two people (0.4%) stopped treatment because of adverse events, one because of decompensated cirrhosis, the other due to newly diagnosed high-grade lymphoma. Overall, 37% of people reported any adverse events. These were mild in the majority of cases. Adverse events were reported by 54% of the ribavirin-treated patients, with 27% requiring dose reduction.

The investigators' analyses failed to identify any significant association between specific DAA regimens and the risk of adverse events. However, ribavirin was associated with a nearly three-fold increased risk of side-effects.

"In real-life conditions, difficult-to-treated HIV/HCV-coinfected patients treated with all-oral DAA combinations reach high rates of SVR12, similar to those achieved by monoinfected patients in such conditions," conclude the authors.

"Future drugs should be focused on reducing the risk of drug-drug interactions, along with an improvement in efficacy in patients with increased liver stiffness."

Reference

Mínguez C et al. *Interferon-free therapy for treating HCV in difficult-to-treat HIV-coinfected patients as implemented in routine medical practice*. AIDS, online edition. DOI: 10.1097/QAD/0000000000001699 (2018).

January 17, 2018
Latimes.com

Mathilde Krim, Who Galvanized Worldwide Support in The Fight Against AIDS, Dies At 91

By Steve Marble

Mathilde Krim's rise to prominence as an AIDS researcher and global crusader in the early fight against the deadly disease began with a simple phone call from a friend.

A physician in New York's Greenwich Village, Joseph Sonnabend, told the scientist about the strangely similar symptoms in many of his gay male patients — swollen lymph glades, enlarged spleens, stubborn infections. Their immune systems were hopelessly compromised.

Within months, all of the affected patients had died.

"It was totally mind-blowing for a scientist who thinks she knows something to realize that, here in the middle of New York in the 20th century, a new disease could occur," Krim told the Los Angeles Times in a 2000 interview.

Bearing witness to the early ravages of the mysterious syndrome, the geneticist and virologist threw herself into the fight against AIDS and emerged a fierce crusader for showing compassion and empathy for those whose lives were touched by the disease.

A lifelong activist who was shaped first by the Holocaust and then the AIDS epidemic, Krim died Monday at her home in Kings Point, N.Y.. She was 91.

"Mathilde Krim exemplified the notion that a single person can change the world," tweeted Elton John, who worked alongside Krim to raise funds for AIDS research. "She committed the entirety of her life to finding a cure and treatment for HIV."

Robert Frost, the chief executive for the Foundation for AIDS Research, or amfAR, said although he was gripped with a "penetrating sadness," he was heartened by the sheer scope of Krim's life work.

"There is joy to be found in knowing that so many people alive today literally owe their lives to this great woman."

Born in Como, Italy, on July 9, 1926, Krim grew up in Switzerland. Though initially shielded from the atrocities of World War II, Krim was forever touched by newsreels that showed the liberation of Nazi death camps and the skeletal figures who emerged.

"I confronted the reality that racism is murderous," she told The Times. "I learned a lesson there."

Appalled, she joined a Zionist underground movement and helped smuggle guns across the Swiss-French border for its members. She also pursued a career as a scientist, eventually earning a doctorate in genetics at the University of Geneva.

After marrying a medical student, Krim told her parents she was converting to Judaism and moving to Israel. She said her parents, who she'd long suspected were at least mildly anti-Semitic, were horrified.

The marriage ended in divorce, and Krim moved to New York several years later after marrying Arthur Krim, who would become chairman of United Artists. Mathilde Krim initially accepted a position at Cornell Medical School to study cancer viruses and then became a researcher at the Sloan Kettering Institute for Cancer Research in New York.

Both fascinated and horrified by the mysterious virus that was taking a heavy a toll on gay communities across America, Krim sought to both understand the disease and raise funds for better and quicker research. She quickly saw what a lonely fight it would be.

When Krim tried to rally scientists, corporate donors and government officials, most turned away. Time and again people told her the disease was striking "those who deserved it."

"In those early days, they were literally dying in the streets," Krim said. "[Gay men who had AIDS] lost their jobs, their apartments — their families turned away from them. It turned my stomach. It really impacted me, and I decided this was something not to be tolerated."

She watched angrily, helplessly as AIDS started showing up in other populations: hemophiliacs, intravenous drug users, blood transfusion recipients and newborns.

Still, the public and many government officials seemed surprisingly unconcerned. In 1983, Krim took matters into her own hands. She established the AIDS Medical Foundation to serve as a "scientific venture capitalist."

It would provide seed money to researchers with innovative AIDS-related theories and technologies — scientists who, in many cases, had been turned down for funding by government agencies. She also hoped her organization could educate the public about the disease and would effectively lobby for legal protection of the afflicted.

Arthur Krim tendered the organization's first capital: about $100,000. Within 90 days, Mathilde Krim raised $550,000 more.

Soon, a growing number of researchers turned to her organization for funding. Krim began putting in 16- to 18-hour workdays, seven days a week, to oversee operations; visit hospices, clinics and adult daycare centers; keep current with scientific literature; and host fundraisers.

One of her earlier backers — and a co-founder of amfAR — was actress Elizabeth Taylor.

"Elizabeth Taylor got AIDS [talked about] on 'Entertainment Tonight,' and you can't underestimate the value of that kind of exposure," said Randy Shilts, who wrote the landmark chronicle "And the Band Played On: Politics, People, and the AIDS Epidemic." "It made the disease something that respectable people could talk about."

In 2000, Krim was awarded the Presidential Medal of Freedom, the highest civilian honor in the U.S.

Krim is survived by a daughter, Daphna; two grandchildren, Robert and Amanda; and a sister, Maria Jonzier.