Mini-Review

A global initiative on local preparation of virus inactivated cryoprecipitate in developing countries

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Abstract: In developing countries, treatment of patients with bleeding disorders is inadequate or absent and the dramatic situation has not changed significantly during the past 20 to 30 years despite several initiatives set up by different national and international organizations. Past experience has shown that industrially manufactured clotting factor concentrates cannot solve these problems in developing countries, if they are used as the sole means in the treatment of patients with bleeding disorders. Recently, significant developments have occurred which have the potential to change the disastrous situation in therapy delivery to "hemophiliacs" in developing countries: blood systems (with blood services and blood centers) in many resource limited countries have tangibly improved and novel technologies for viral inactivation of blood components have been developed and are marketed [amotosalen, riboflavin, solvent-detergent (SD), etc.]. In a few developing countries, local preparation of virus inactivated cryoprecipitate (Cryo-VI) has been introduced and Cryo-VI has proven to be a safe, effective therapeutic for patients with bleeding disorders, at an affordable cost. But the use of VI-technology to render cryoprecipitate safe remains very limited; therefore, major coordinated actions are needed to promote Cryo-VI in developing countries and to facilitate implementation of local preparation of safe cryoprecipitate. Therefore, a Global Initiative on "local preparation of virus inactivated cryoprecipitate in developing countries" ("Local Cryo-VI in l-HDI") has been launched to improve treatment of patients with bleeding disorders: it is based on collaboration with international partnering organizations (like WHO, ISBT and others) and national stakeholders (e.g., competent authorities, blood suppliers, patient associations). The Global Initiative consists of six core interventions, flanked by additional activities: revise and update existing standards and guidelines on "anti-hemophilic" treatment; give high priority in policies and strategies to "Local Cryo-VI in l-HDI"; organize strong advocacy; run a Pilot Project (PP) in several pilot sites; establish an expansion programme; support activities for implementation and sustainability of "Local Cryo-VI in l-HDI". It is complementary to existing relief activities (e.g., product donations) and will result in additional supply of safe and effective haemostatic products to treat patients with bleeding disorders in developing countries. It will also contribute to significantly lower the incidence of inhibitors in previously untreated patients with hemophilia A.

Keywords: Bleeding disorders; hemophilia; virus inactivated cryoprecipitate; developing countries; global initiative; local preparation of hemostatic products; product supply; inhibitors

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Introduction

Developing countries are characterized by a low Human Development Index (HDI; score less than 0.600 according to UN definition) and they are all resource limited.

Treatment of patients in countries with a low HDI (l-HDI) is in general insufficient, inappropriate or simply

absent. This applies particularly to patients with hemophilia A, von Willebrand disease or fibrinogen abnormalities (these patients are called hereafter: "hemophiliacs").

The trigger for the Global Initiative on local preparation of virus inactivated cryoprecipitate in developing countries ("Local Cryo-VI in l-HDI") has been the continuing disastrous situation for hemophiliacs, suffering pain, crippling and death.

In l-HDI countries, hemophilia treatment has many deficiencies and the most important are related to "anti-hemophilic" products:

- Supplies (meaning availability as well as accessibility);
- Costs (for purchasing clotting factor concentrates, CFC; meaning affordability);
- Inhibitors (adverse reactions in hemophiliacs following administration of haemostatic products).

For the moment, "Local Cryo-VI in l-HDI" appears to be the only way to solve in a sustainable way these problems, at least in parts, waiting for better times to come in the developing world. For hemophiliacs, it would reduce suffering and crippling and allow them to survive until CFC become available, hopefully.

Safe cryo is available for several years now as Cryo-SD/F (Cryoprecipitate, Solvent-Detergent treatment and Filtration): "native" cryo undergoes viral inactivation with a medical device marketed by VIPS company under the name "Cryo-SD/F®" (1,2), "killing" relevant viruses causing transfusion transmissible infections (TTI, like HBV, HCV, HIV), if they are present.

Despite undisputed records of safety and quality, Cryo-SD/F is not being used widely up until now. In order to extend this technology into developing countries, a worldwide movement has been organized end of 2016. It is called "The Global Initiative on local preparation of virus inactivated cryoprecipitate in developing countries" (abbreviated: "Local Cryo-VI in l-HDI"). Hereafter, this comprehensive international project is described in more details.

Global movement based on a multi-modular initiative

It is well known that there is a significant volume of plasma in the developing world that is not used for the treatment of patients. Plasma contains many valuable proteins, including clotting factors in its cryoprecipitable fraction.

In developing countries, huge amounts of plasma are wasted, either when whole blood is transfused (instead of packed red cells) or when plasma is discarded (when it is not needed for fresh frozen plasma transfusions).

The primary goal of the Global Initiative is to promote and to propagate local preparation of safe and effective products (e.g., virus inactivated cryoprecipitate) to treat bleeding disorders in developing countries and to facilitate implementation as well as ensure sustainability.

This Global Initiative comprises the following core interventions:

(I) Revise and update standards and guidelines on "anti-hemophilic" therapy;
(II) Give high priority in policies and strategies to "Local Cryo-VI in l-HDI";
(III) Organize advocacy and promotion;
(IV) Run a Pilot Project (PP);
(V) Establish an expansion programme;
(VI) Support l-HDI in their activities for implementation and maintenance of "Local Cryo-VI".

Besides the central interventions, several flanking activities have been developed to increase the chances that the Global Initiative will result in additional supply of safe and effective products to treat patients with bleeding disorders in developing countries.

Intervention 1

Revise and update standards and guidelines on treatment of patients with bleeding disorders in developing countries

There are multiple guidelines on the treatment of patients with bleeding disorders available from different international organizations: World Health Organization (WHO), Council of Europe/European Directorate for Quality of Medicines & Health Care (CofE/EDQM), World Federation of Hemophilia (WFH)… In addition, there are many guidelines from national organizations (medical societies, patient organizations, regulatory authorities, social security agencies, health insurance companies…).

Most of them are derived or take into consideration the guidelines published by WFH (3): these have the widest impact and are considered by many as state-of-the-art. Therefore, it is of paramount importance that "WFH Guidelines on the Management of Hemophilia" contain complete and recent scientific knowledge in the field. The actual 2nd edition of these guidelines is not comprehensive as it does not mention Cryo-VI as a safe therapeutic product and does not recommend it as an alternative if CFC are

unavailable.

Anyway, guidance on the treatment of patients with bleeding disorders should no longer be general and universal ("one size does not fit all"), but they need pragmatic stratification for:

- Categories of *countries* (there are considerable differences between jurisdictions in the developed and the developing world, coming with such an amplitude that one single set of recommendations cannot serve them all adequately);
- Groups of *patients* (there are individuals with inherited bleeding disorders like hemophilia, VWD and fibrinogen abnormalities, but also those with acquired bleeding disorders like fibrinogen consumption/depletion in women with complicated child delivery resulting in impaired hemostasis and increased maternal mortality);
- Classes of *products* (clotting factor concentrates and other hemostatic products, including virus inactivated blood components, such as FFP-VI and Cryo-VI);
- Sub-classes of *medicinal products* (plasma-derived and recombinant; containing full-length, B-domain deleted and fusion clotting factors, …);
- Types of *treatment protocols* (prophylactic and continuous treatment schemes, on-demand and mixed regimens);
- Sets of *dosage* (high dose, intermediate dose and low dose protocols);
- Options in *care delivery* (home treatment or self-administration; hospital or health station based substitution therapy, …).

Local preparation of safe and effective hemostatic products in developing countries needs to be added as a new strategic direction, not intended to compete with existing therapeutic approaches, but rather to complete the national schemes (national blood systems).

Upon request from the Global Initiative, several international organizations dealing with blood matters and blood products have started to revise and update their clinical recommendations and guidelines.

The Council Europe/EDQM has closed its consultation round for the revision of its "Guide to the preparation, use and quality assurance of blood components" (4) and is about to publish its 19th edition. The coming revised edition of the "Guide" will have in Chapter 5—Components Monographs—Part D: Plasma Products, a separate section on Cryoprecipitate-pathogen reduced.

The revised "Guide" will have a direct impact on the Member States of the European Union (EU) as a recent Commission Directive (EU) 2016/1214 of 25 July 2016 (5) amending Directive 2005/62/EC as regards quality system standards and specifications for blood establishments makes this "Guide" legally binding for the EU Member States. And it should be reminded that in Whereas [29] of the EU "Mother" Blood Directive 2002/98/EC (6) it is stated that "it should also be taken in due account scientific advances in the detection, inactivation and elimination of pathogens which can be transmitted via transfusion".

The International Society of Blood Transfusion (ISBT) has worked intensively on "Cryo-VI" through its Working Party on Global Blood Safety (WP on GBS). A comprehensive set of recommendations supporting local preparation of hemostatic products in developing countries has been drafted by the WP and sent recently to ISBT Board of Directors for further action.

Concerning WHO treatment guidelines given in the Handbook of Appropriate Clinical Use of Blood (7) the revision process is about to start and transfusion medicine specialists of WHO Expert Panel in Blood Transfusion will advocate for the incorporation of Cryo-VI in the revised clinical guidelines.

The Global Initiative has contributed to revisions and updates of the mentioned international organizations. In a next step, prominent national standards and guidelines will be on the scope of the Global Initiative.

Intervention 2

Give high priority in policies and strategies to local preparation of virus inactivated cryoprecipitate in developing countries

Under normal circumstances, policies on health care issues are drafted and approved, standards and guidelines are elaborated accordingly and translate policies into requirements and technical details. Strategies and action plans are developed for implementation, taking these into account.

In l-HDI, this logical order is not always followed. It is not seldom that standards and guidelines from international bodies or from developed countries are taken up, although it may well be that they are not suitable for the given developing country.

WFH policies are seen by many as the reference to follow and many countries (including developing ones) have brought their national policies on hemophilia treatment

in line with those published by WFH. The same applies for national strategies to administer "anti-hemophilic treatment" according to what WFH is propagating for the field.

Most experts agree that "The principles of management of hemophilia are the same all over the world". Nevertheless, taking into account the realities in developing countries a "dual set of doses" is recommended for CFC replacement therapy (3).

With the advent of new technologies and the changing environment in the blood sector in developing countries, the Global Initiative on "Local Cryo-VI in l-HDI" is soliciting a justified differentiation for hemostatic products to be used in developing countries for the treatment of bleeding disorders: a "dual set of products" is necessary to adequately address existing deficiencies like it has been done with a "dual set of doses".

A paradigm shift is urgently needed, away from exclusivity and predominance of CFC.

Past experience has shown that the existing problems in developing countries cannot be solved solely with imported products. Local preparation of hemostatic products (like Cryo-VI) has a significant potential to "buffer" the shortages in product supply.

The ultimate goal for low or moderate HDI countries in the treatment of patients with bleeding disorders remains identical with high or very high HDI countries: "Treatment for All" (8).

Nonetheless, developing countries can most probably achieve this aim only with a different road map as compared to developed countries, in terms of time lines, means and activities.

Developing countries may need an additional, temporary and intermediate step, using lower doses and locally prepared products. The final goal in substitution therapy will remain unchanged, also for developing countries: ultimately, they strive to achieve home treatment and prophylaxis, relying on sufficient supply with high-end products (recombinant or plasma-derived CFC of the latest generations).

For the moment and probably for many years to come, developing countries will have to cross a transition period, using locally prepared safe and effective hemostatic products like Cryo-VI before they can aspire for CFC. In any case, the supply source needs to be sustainable and continual in developing countries and this can only be achieved with local preparation of needed therapeutic products.

Even in the most resource limited countries, activities are undertaken to collect whole blood, to separate blood donations into blood components and to supply hospitals for their transfusion needs. Therefore, in all resource limited countries blood center activities exist and plasma is available (as it is not needed for direct transfusion). According to WHO's Global Status Report on Blood Safety and Availability 2016 (9), "native" cryoprecipitate is used widely, mostly in developing countries (as no other "anti-hemophilic" products are available), but also in some developed countries (for certain defined conditions).

"Native" cryo can be subject to viral inactivation to render this blood component safe, stripping off the risk of TTI with relevant viruses such as HBV, HCV and HIV.

Cryo-VI can be seen as a spin-off product of activities in blood centers and there are realistic chances that Cryo-VI can be supplied without disruption which is not the case with CFC (purchased or donated).

This reality needs to be seen and emphasized and, most importantly, be reflected in policies, strategies, standards, guidelines, recommendations and others.

The Global Initiative on "Local Cryo-VI in l-HDI" is cooperating with WHO and its worldwide presence and uncontested authority will largely contribute to exercise influence with governments to include Cryo-VI in their health programmes and product portfolios.

Intervention 3

Organize advocacy and promotion for local preparation of virus inactivated cryoprecipitate in developing countries

For decades, cryoprecipitate has been extensively used to treat bleeding patients and it continues to be used widely (9). Almost always, cryo is used in its "native" form bearing the risk of TTI. When the HIV pandemic struck the hemophilia community in the 1990s, the safety record of cryo was severely tainted, its reputation damaged and its therapeutic values over-shadowed.

With viral inactivation technology becoming available, cryoprecipitate can be rendered safe and be a precious product for hemophilia treatment in developing countries, as Cryo-VI.

Unfortunately, correct information and messages have not reached many l-HDI and it is precisely here that the Global Initiative will act as leverage for advocacy of Cryo-VI in developing countries: promoting the advantages of Cryo-VI with governments, regulatory authorities, health insurances, medical societies, patient associations, blood

suppliers, hospitals, etc… is of paramount importance to roll-out Cryo-SD/F.

SD is a VI-technology which is highly effective in eliminating the risk of TTI through relevant viruses (10,11). Also, it relies on working methods which are routine in blood centers, uses a closed system of interconnected plastic bags, is technically simple, easily implementable and robust, is cost-effective and results in safe and effective products ready to be used for patients needing FVIII, WF or FI.

Through the Global Initiative the benefits and advantages of Cryo-SD/F are presented to the stakeholders in the blood system in a given developing country, through channels which have proven efficient. It is common practice to lobby with governments using international standards and guidelines. However, WFH guidelines (backed also by ISTH, International Society of Thrombosis and Hemostasis) are far from being optimal to convince governments of the added value in using Cryo-SD/F. They mention cryoprecipitate only briefly, express warnings about the risk of TTI, do not make a difference between "native" and virus inactivated cryo, do not mention Cryo-VI at all as a possible alternative when CFC are unavailable.

The Global Initiative on "Local Cryo-VI" has started with education and advocacy in close collaboration with WHO: Blood Safety Programme (BSP), Regional Offices as well as Country Offices.

Intervention 4

Run a PP to field test existing technologies for viral inactivation of cryoprecipitate and to demonstrate feasibility and sustainability

A feasibility study is undertaken for the implementation of SD/filtration (SD/F) technology on cryoprecipitate in selected pilot sites which are representative to some degree of the situation in resource limited countries.

The PP is conducted in blood centers in six developing countries on three continents. Blood centers have been recruited for the PP and they are located in Africa, Asia and Latin America.

Almost all equipment needed is in place in the selected blood establishments as they are functioning as major blood transfusion centers in their countries: blood donors and their donations constitute the starting point for multiple different processes (collection, testing, processing, storage), ending with distribution of blood products requested by hospitals.

After careful analysis, the Global Initiative has selected the pilot sites in developing countries responding to predefined criteria and in such a way to be representative for the conditions to be found in developing countries when implementing and maintaining activities necessary for "Local Cryo-VI". Level of quality management as well as strategic position of the pilot sites in the national blood systems have been important selection criteria for the inclusion of these blood centers into the PP.

For each pilot site, an individual logical framework has been elaborated, including aims, objectives, activities, hypotheses, prerequisites, risks as well as detailed budget lines. Production targets are set following a short assessment: the volume of locally prepared Cryo-SD/F is largely dependent on limitations in the PP as well as potential need and use by local patients.

As premises, equipment and staff are already in place, the budgets needed to finance the PP are covering essentially:

- Training and education (of staff in blood centers, but also of clinicians prescribing hemostatic products);
- Quality management and work flows (when adjustments are needed);
- Personnel (when additional staff is required);
- Material (mainly kits for the preparation of locally prepared Cryo-SD/F).

Sufficient funds have been made available to run all activities related to the PP during a defined period of time.

As regulatory affairs in developing are not always seen as a priority and not handled in "fast track" mode, the start of PP is scheduled for the beginning of 2018.

Intervention 5

Establish an expansion programme for local preparation of virus inactivated cryoprecipitate in developing countries

Based on the experience and the lessons from the PP, a comprehensive programme is needed to roll out "Local Cryo-VI" inside the countries participating in the PP.

Further on, around the countries contributing to the PP, the same roll-out programme will help penetrating the region and it is planned in collaboration with WHO: WHO HQ in Geneva, Switzerland is a vital cornerstone with its BSP.

Complementing BSP, WHO Regional Offices play also a decisive role. Especially, PAHO (Pan American Health Organization), WPRO (Western Pacific), AFRO (Africa) and EMRO (Eastern Mediterranean) will be crucial

partners in this regard, in extending technologies for viral inactivation of cryoprecipitate to interested developing countries and blood centers there.

WHO's Network of Collaborating Blood Centers has a significant potential to support expansion of VI-technologies into larger regions of developing countries, most in need of Cryo-SD/F.

If feasible, a WHO Global Consultation and/or WHO Global Forum on "Local Cryo-VI in l-HDI" will boost expansion of it in developing countries.

WHO Regional Consultations and Workshops are very effective tools for further extension and deeper penetration into developing countries.

It does not suffice to bring to developing countries knowhow and training on local preparation of hemostatic products which are effective and safe (through pathogen reduction): the flanking activities of the Global Initiative will facilitate implementation, but also sustainability.

Along the same line, ISBT will be instrumental in spreading knowledge and practical know-how on "Local Cryo-VI" (e.g., Academy Days, special sessions dedicated to l-HDI during its congresses, sponsored events…). ISBT has signaled that it is willing to give developing countries a voice in its activities and to support the use of Cryo-VI and related activities.

It is of utmost importance that at political level this new approach in the treatment of patients with bleeding disorders in developing countries is perfectly understood, well accepted, actively supported and clearly translated into relevant policies, strategies and action plans.

Above all, the national blood policy in a country needs to embrace Cryo-VI. Updating of relevant policy documents is essential and these texts should be based on and in accordance with WHO's templates.

For this purpose, the Global Initiative will organize advocacy with the competent health authorities in developing countries to actively support local preparation of Cryo-VI in the blood centers.

Also, usage of these products needs to be promoted and facilitated. Medical requests and prescriptions of Cryo-VI for patients with bleeding disorders are to be stimulated.

National hemophilia associations/societies in developing countries will play an important role in strengthening both arms of the blood system (production and usage). Targeted lobbying by patient organizations is an important part of the Global Initiative and it constitutes one of the flanking activities.

When advocating in the resource limited countries, it is necessary:

(I) To build on existing national blood systems;
(II) To improve blood policies and extent their coverage to Cryo-VI;
(III) To incorporate additional safe blood products into national blood programmes;
(IV) To facilitate local preparation of hemostatic products treated by VI-technologies through revised national blood plans, quality manuals, standards and guidelines.

In addition, national patient organizations need to get the skills and the arguments to present Cryo-VI to the key stakeholders in their blood systems. WFH's Advocacy in Action (AiA) Program is well suited to assist its NMOs in developing and strengthening their advocacy skills, and to provide tools to conduct successful advocacy projects and activities.

The expansion of "Local Cryo-VI in HDI" is a stepwise and time consuming process. If done in collaboration with international partners, the Global Initiative will succeed in many resource-limited countries.

Intervention 6

Assist and support developing countries in implementing and maintaining their activities for local preparation of virus inactivated cryoprecipitate

In developing countries, limited financial resources make many medical interventions impossible or unsustainable.

This fact also applies to the treatment of patients with bleeding disorders where medical products (whether plasma-derived or recombinant) are needed.

In order to render a new programme sustainable in a country, governments need to create a dedicated position in their regular budgets, in this case for Cryo-VI.

The Global Initiative will develop a costing model to calculate and estimate expenses related to VI-technologies, allowing l-HDI countries to anticipate and manage reasonably inherent costs.

Durability needs to be built into the expansion activities, right from the beginning, taking into account future needs for resources, whether financial, human or material.

WHO Regional Offices as well as WHO Country Offices in those developing countries which are possible candidates for "Local Cryo-SD/F" have ample experience in how to deal with questions around sustainability.

Implementing an activity in a developing country is not

necessarily complicated and problematic, maintaining it is always a challenge. Therefore, existing aid programmes in the blood arena (like from World Bank, PEPFAR, Global Fund-ATM, …) need to be included when the preparations and planning are beginning in the context of "Local Cryo-SD/F".

Different NGOs are dedicated to support the blood chain: several organizations give active support to blood centers—financially, with new or used pieces of equipment, training of staff, through external expertise—they also need to become part of the planning.

The Global Initiative will identify active players in the blood system in developing countries and discuss with them how their activities can embrace "Local Cryo-VI".

Flanking activities

The core interventions of the Global initiative are supported by several flanking interventions:

- Twinning programmes between blood centers: cooperation is being arranged between blood establishments in developing countries and blood services/blood centers in developed countries, which have ample expertise in blood processing and which show interest in this kind of development projects;
- Research on new VI-methods: with ISBT and industry support, additional technologies for "Local Cryo-VI" should be developed. Existing VI-technologies which are used to treat platelets and plasma should be made available also for cryoprecipitate. It should be mentioned here that VI-technologies are also being developed for preparation of virus inactivated immunoglobulins and will reach market maturity soon;
- Training Programmes: collaboration with WHO has started to update training materials, to include Cryo-VI and its local production. WHO has different effective tools to administer appropriate education to interested countries, using for example its worldwide Network of Collaborating Centers;
- Advocacy programmes: in partnership with WHO Country Offices and national patient associations in l-HDI, complete and understandable information on "Local Cryo-VI" will be presented to stakeholders in the country to convince them of the multiple benefits and some advantages over CFC;
- Quality schemes for safe cryoprecipitate: IEQAS (International External Quality Assessment Schemes) for therapeutic products are planned by the Global Initiative. This is an innovative approach to make sure that the finished Cryo-SD/F products are safe and effective. WHO's Network of Collaborating Centers or blood centers in the Twinning Programme will play an important role in this quality exercise.

Looking at the entire package (with 6 core interventions flanked by several supporting activities), it is evident that Local Cryo-VI has a fair chance to be used at large scale in developing countries where it can alleviate the dramatic product supply situation of patients with bleeding disorders.

Back in 2014, when the first discussions started about an initiative on Local Cryo-VI, the focus was on supply of anti-hemophilic products, it was about availability, accessibility and affordability in developing countries.

Recently, a critically important aspect has been incorporated into the Global Initiative on "Local Cryo-VI" to tackle the problem of inhibitor formation in previously untreated patients with severe hemophilia A. It proposes to undertake research to reduce the incidence of inhibitors using Cryo-VI during the initial substitution therapy (for the first 10 to 20 injection days).

Summarizing, it can anticipated that the Global Initiative on "Local Cryo-VI" will not only contribute to improve product availability, accessibility and affordability in developing countries, but also to reduce inhibitor formation and to make actual hemophilia treatment safer and more manageable.

Conclusions

Supply, availability, accessibility and affordability of safe and effective hemostatic products in developing countries have been, are being and will continue to be most important challenges for the treatment of patients with abnormal hemostasis. Treatment of patients with bleeding disorders remains poor or absent in resource limited countries. A large majority of hemophiliacs are deprived of any form of safe and effective therapy.

Recently, the situation in the blood sector in many developing countries has changed, with the adoption of blood policies, establishment of blood programmes and organization of blood services. In almost all of these countries exist one functioning National Blood Center and several Regional Blood Centers, which have the capability and capacity to safely produce labile components (including plasma and cryoprecipitate).

In the past few years, new technologies have been developed for viral inactivation of blood components. They have been approved by world-renowned regulatory authorities and have been brought to the market: this is the case for platelets, fresh frozen plasma and also for cryoprecipitate. The latter can be transformed from its "native" form into a secure form, which represents a new generation of cryoprecipitate—Cryo-SD/F.

Taking these developments into account, it is to be concluded that time has come to take advantage of these evolutions, to reduce the disparity between need and supply of hemostatic products in developing countries and also to tackle the devastating inhibitor problematic.

A Global Initiative on local preparation of virus inactivated cryoprecipitate in developing countries ("Local Cryo-VI in l-HDI") has been set up and started end of 2016. It consists of several central interventions: revise and update standards and guidelines on "anti-hemophilic" treatment; give high priority in policies and strategies to "Local Cryo-VI in l-HDI"; organize strong advocacy; run a PP in several pilot sites; establish an expansion programme; support activities for implementation and sustainability of "Local Cryo-VI in l-HDI".

These central activities are flanked by additional interventions to reach necessary robustness and ensure sustainability: twinning programmes between blood centers; research on new VI-methods; training programmes; advocacy programmes; International External Quality Assessment Schemes for therapeutic products.

The primary goal of the Global Initiative is to come closer to "Treatment for All". In a stepwise approach it will make sure that it is well understood in low-HDI countries that starting material is available in sufficient amounts in the form of plasma, that cryoprecipitate can be prepared from it and that viral inactivation can make it safe for transfusion transmissible infections (above all, viral TTI like HBV, HCV and HIV).

Local preparation of Cryo-SD/F can make available substantial amounts of highly effective hemostatic products and holds a realistic commitment to improve product supply in a sustainable way. Cryo-SD/F is a rather inexpensive therapeutic as compared to clotting factor concentrates (CFC). The ultimate product goal for treatment of patients with bleeding disorders will remain CFC, whereas treatment with Cryo-VI may be seen as a temporary step until CFC become available in sufficient amounts in l-HDI countries.

The Global Initiative on "Local of Cryo-VI in l-HDI" has the potential to significantly alleviate the desperate supply situation of patients with bleeding disorders in developing countries—it needs support to prove its ambitions for inducing major change in resource limited countries.

Recently, another important aspect has been incorporated into the Global Initiative. Inhibitor formation in previously untreated patients with severe hemophilia A constitutes, together with supply issues, the single most important threat for hemophiliacs. Cryoprecipitate is coming with a significantly lower inhibitor attack rate (some 5%) as compared to CFC (at least 25% to 35%, under unfavorable conditions even more). It is proposed to consider using for previously untreated patients with severe hemophilia A Cryo-SD/F during the initial treatment (for the first 10–20 infusion days). "Local of Cryo-VI in l-HDI" has the potential to significantly reduce the problem of inhibitors which is particularly devastating in hemophiliacs in developing countries as there is no realistic way to treat these patients. The only pragmatic approach to protect hemophiliacs from inhibitors is preventing or at least reducing their formation.

Finally, in combining issues related to product supply and inhibitor formation, the Global Initiative on "Local Cryo-VI" represents real progress in the treatment of patients with bleeding disorders in resource limited countries. In fact, it appears that Cryo-SD/F is the only realistic and reasonable approach for the moment in the developing world.

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