5. IRON OVERLOAD IN THALASSAEMIA: ITS MONITORING AND TREATMENT TIF'S PERSPECTIVE

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INTRODUCTION

Iron Toxicity

Iron toxicity to vital organs represents, along with severe anaemia, the basic pathophysiological consequences of ineffective erythropoiesis in thalassaemia. As such reduction of iron load is a major therapeutic target for thalassaemia patients1. Iron accumulates because of increased absorption of dietary iron from the gut in non-transfusion dependent thalassaemia (NTDT), such as β-thalassaemia intermedia and α-thalassaemia, and more importantly because of repetitive blood transfusions due to the breakdown of transfused red blood cells in transfusion-dependent thalassaemia (TDT). Normally, only 1-2 mg of iron is absorbed from dietary sources daily and the same amount is excreted via the stools, thus preserving iron homeostasis. In contrast, each unit of transfused blood contains 200 mg of iron (0.47mg/ml), and thus regularly transfused patients inevitably develop iron overload. Iron excess saturates the binding and transferring capacity of the iron-binding protein transferrin, leading to the development of non-transferrin bound iron (NTBI) [1]. Contrary to protein-bound iron that is stored mainly in the liver and is not toxic, NTBI, and especially the species known as labile plasma iron (LPI), is taken up by cells, such as cardiomyocytes, hepatocytes and the cells of endocrine glands, in an uncontrolled manner, leading to oxidative organelle damage, cell dysfunction and death. As a result, serious complications develop, which if not detected early and managed appropriately, may become debilitating and cause premature death in TDT patients. In NTDT, iron overload due to increased iron absorption develops at a much slower rate leading to complications later in life, mostly in the second and third decades [2].

The major organs affected by iron toxicity are:

- *The **HEART**, in which iron toxicity manifests as cardiac dysfunction, heart failure and arrhythmia. Iron overload cardiomyopathy remains the main cause of death in TDT patients, even though it has been considerably reduced under current monitoring and treatment regimens [3, 4].*
- *The **LIVER**, in which damaged hepatocytes are replaced over time by fibrous tissue, increasing substantially the risk of cirrhosis and hepatocellular cancer, which represents an important cause of morbidity and mortality in TDT patients especially in the older age group of patients [5].*
- ***ENDOCRINE GLANDS** are affected in varying degrees in the majority of thalassaemia patients. Iron overload causes several endocrine disorders, either directly or indirectly, through the hypothalamus/pituitary axis including growth retardation, hypogonadism, hypothyroidism, hypoparathyroidism and diabetes mellitus [6,7,8].*

Controlling Iron Toxicity

Developing a protocol to control the toxic effects of iron overload requires the adoption of two measures:

1. Monitoring the accumulation of iron, thus allowing for the early detection of iron overload as well as the follow-up of iron chelation therapy. This is achieved by a series of tests, both biochemical (mainly serum ferritin and transferrin saturation) and imaging (MRI techniques to measure tissue iron content).
2. *Removing free iron by drugs* that bind to it and facilitate its excretion through urine or faeces. These substances are known as chelating agents and the only way to prevent tissue damage is by the daily consumption of these agents. The chelating agents in common use are:
    - Desferrioxamine (DFO), a parenteral medication administered by slow subcutaneous infusion, ideally over 24 hours, but for practical purposes over 10-12 hours. Such an administration requires a portable infusion pump along with reconstitution and dilution of the powdered substance at home. In a hospital setting, DFO may be given intravenously as a continuous infusion, usually as a rescue treatment in severe iron overload, especially when severe heart failure symptoms develop.
    - Deferiprone (DFP) is an orally administered medication given in three divided doses.
    - Deferasirox (DFX) is another orally administered medication given on a once-daily basis.

Combinations of these drugs are also used, especially when iron overload is significant and does not respond well to monotherapy [9].

It has also been amply demonstrated that well managed iron chelation can effectively reduce iron and its toxic effects. In a study from Turkey comparing the impact of using MRI techniques to guide iron chelation therapy, from 2006 to 2019, patients with safe LIC values (< 7 mg/g dw) increased from 57 to 77%, and safe cT2* values (> 20 ms) increased from 72 to 86% [10].

Adjuvants to chelation therapy, enhancing the effect of the aforementioned chelating agents, have been reported, although not universally used and not established in clinical practice. Eltrombopag combined with deferasirox and amlodipine combined with standard chelation regimens are two examples [11,12, 13].

Determinants of Effective Iron Overload Monitoring and Treatment

Effective control of iron overload is hampered by factors, which are dependent on organisational and financial support, but also on awareness among physicians and patients. These factors include:

- Availability of reliable iron monitoring tools. In many treatment centres, only serum ferritin is used to monitor iron overload, which can be influenced by other factors, such as liver disease and inflammation and is not a reliable surrogate or cardiac iron content. Serum biomarkers of iron loading especially affecting the heart such as ANP (atrial natriuretic peptide); BNP (brain natriuretic peptide); GDF-15 (Growth Differentiation Factor 15); and NT-pro-BNP (N-terminal pro-brain natriuretic peptide) as well as imaging biomarkers using MRI, have been extensively studied for the timely diagnosis of danger to vital organs [14]. Expensive technologies, such as MRI, are required for the reliable detection and monitoring of iron accumulation in vital organs, including heart and liver. In addition, iron monitoring should be part of a well-structured multidisciplinary care (MDC) plan carried out by a team that, besides the thalassaemia-treating physician, includes at least a cardiologist, an endocrinologist and a

hepatologist, along with psychosocial support services. *For more information see Chapter on Multidisciplinary Care.*

- Availability of iron chelation agents. Availability may be hampered by lack of drug licensing or approval by local regulatory authorities, impaired procurement by budgetary restrictions that limit supplies, or lack of coverage by local insurance systems that imposes out-of-pocket payment by the patients [15]. Several countries report to TIF a lack of constant supply of the various chelating agents. Discontinuation of a drug leads to the discontinuation of iron chelation an increase in iron overload and toxicity. One country that reports this as a major factor affecting patient outcomes is Iran and this may be affected by the economic embargo, which is currently in effect, even though there is a local production of chelating agents, but raw materials are imported. [information from an October 2022 meeting with HCPs and patients]. The quality of locally produced drugs is questioned by both patients and physicians.
- Professional knowledge and awareness of evidence-based practices and standards of care. Inexperience and inadequate knowledge of physicians is a phenomenon that is not well documented in scientific publications but is common where rare conditions are concerned [16].
- Adherence to prescribed treatment. Lack of patients' adherence to prescribed chelation regimens [17]. The requirement is for daily chelation since even short interruptions lead to the exposure of cells to free iron radicals. Various interventions have been suggested to reduce this phenomenon, mainly relying on psychosocial support and patient participation in management decisions. Such patient support is lacking in many clinics globally. Particular emphasis is given on this parameter in this chapter, being part of a review study compiled by a patient-oriented organisation – TIF.

Global Inequalities in Iron Overload Monitoring and Treatment

There are significant inequalities in the care of thalassaemia patients, which in turn result in variable patient outcomes. In countries where optimal care is available and accessible, the effective control of iron toxicity has led to a dramatic increase in patients' survival [18], leading to the gradual rise of an ageing patient population who are now facing new age-related complications [19]. Given the fact that 80% of thalassaemia patients live in limited-resource countries where state-of-art healthcare may not be the norm, the Thalassaemia International Federation (TIF) has conducted a search into the availability of iron overload monitoring and treatment resources in TIF member countries, to identify unmet needs and provide member organisations and health authorities with advice on policy making.

Measuring performance and outcomes was based on information provided by local service providers, unless official reports at health administration level have been published. At this point, it should be stressed that published reports on thalassaemia care and outcomes are generally confined to few countries and isolated centres, mostly those with good results to report. Evidence on accessibility and affordability of effective iron overload control remains largely unknown for thousands of thalassaemia patients who face the risk of premature death and poor quality of life due to lack of access to quality services and professional expertise.

METHODOLOGY AND RESULTS

The investigation of availability and effectiveness of iron overload control is a challenge, which is met by using more than one source of information. A literature search regarding both monitoring and the availability of iron chelation was supplemented by reports collected from TIF delegation visits as well as reports sent by member associations. Countries, which at the time of writing were in a state of political instability or war have been excluded. These countries include Syria, Libya, Yemen and Iraq. Since, however, they have a high prevalence of thalassaemia syndromes, the situation in these territories is analysed separately, and TIF's efforts to alleviate their situation is discussed. A total of 56 countries were investigated by the methods described below [References 19-50].

In this global study, TIF has collected data covering 3 domains:

- Availability of essential resources and services for controlling iron overload, including monitoring and chelation, in high prevalence countries.
- Effectiveness of iron chelation.
- Patient adherence.

The methodology followed for each domain and the generated results are reported in detail as follows:

Availability

The main elements of this investigation include (i) whether the currently established chelating agents are approved and available to patients free of charge; (ii) whether monitoring is also available and free; (iii) whether monitoring is carried out in a regular manner so as to be effective in predicting complications. The compounded results of this investigation have resulted in the development of a scoring system to describe the availability of the basic components of iron overload control. This scoring system is summarized below in Table 1(i). A total maximum score of 45 indicates a country that provides the means for optimal control of iron overload monitoring and treatment.

Table 1. Scoring methodology for iron load monitoring (s. Ferritin/MRI) and treatment (chelation drugs)

Scoring Methodology 3 units are given for each available drug 3 units are given for iron chelation provision free of charge	
Number of Available Drugs (3 are authorised*)	**Score**
If only 3	9 (3x3)
If only 2	6 (3 x 2)
If only 1	3 (3 x 1)
Cost of Provided Drugs	**Score**
All 3 free	9
Only two provided free	6
Only one provided free	3

Co-Payment Policies	Score
Chelators paid by patients	0
Co-payment is the policy for one chelator	3
Co-payment is the policy for two chelators	1
Co-payment is the policy for three chelators	0
Serum Ferritin Testing Frequency	**Score**
Every 3 months	9
Every 6 months	6
Annually	3
Longer than annually	0
MRI Testing Frequency	**Score**
Annually	9
Biennially (every 2 years)	3
Longer than biennially (every 2 years)	0
MRI Testing Cost	**Score**
Free for all patients	9
Less than 10% co-payment (of full cost)	6
10% - 30% co-payment (of full cost)	3
30% - 50% co-payment (of full cost)	1
More than 50% co-payment (of full cost)	0

**Desferrioxamine, Deferiprone and Deferasirox*

***In the absence of quality assured measurements the score is zero, but, unfortunately, it was not possible to retrieve reliable information on MRI/MRI software validation.*

****Near ideal optimal services for iron monitoring and treatment is scored with 45 units.*

Based on that scoring exercise (Table 1), grading of availability of iron load monitoring and treatment was attempted (Table 2).

Table 2. Scoring and grades

SCORE	GRADE
36	A
20-45	B
10-20	C
<10	D

Countries scoring >36 units are graded as **A** and anticipated based on their high level of services' availability to provide near optimal chelation monitoring and chelation therapy. Similarly, **B** grade countries can be considered as providing adequate services and which with more efforts could reach near optimal levels. Countries graded **C** and **D** are those that need to commit considerably more efforts and focus on improvements and are anticipated to have a young patient population, thus lower survival rates and higher morbidity levels.

This score, however, does not take into consideration factors related to effectiveness and others such as physician compliance with guidelines or patient adherence to prescribed medications. MDC is not guaranteed either. For these reasons, **this scoring system can only estimate the *opportunity* for quality patient care**. (For the above additional important factors, a separate in-depth analysis is provided in the respective chapters on Multidisciplinary Care and Reference/Expert Centres of this Report).

Using the above scoring system, the various countries / territories have been graded between A-D according to their score with respect to the availability of services as noted in Table 2 and shown in Table 3 below:

Table 3. Availability of monitoring for and treatment of iron overload

Country	HDI	Grading Availability	Country	HDI	Grading Availability
Austria	VH	B	**Jordan**	H	A
Bulgaria	VH	A	**Lebanon**	H	A
Cyprus	VH	A	**Tunisia**	H	B
France	VH	A	**Maldives**	H	B
Germany	VH	A	**Sri Lanka**	H	B
Greece	VH	A	**Thailand**	H	A
Israel	VH	A	**China**	H	D
Italy	VH	A	**Taiwan, China**	VH	B
Netherland	VH	A	**Brazil**	H	A
Romania	VH	B	**Trinidad & Tobago**	H	B
Spain	VH	A	**Mauritius**	H	C
United Kingdom	VH	A	**Algeria**	H	D
Sweden	VH	B	**South Africa**	M	D
Saudi Arabia	VH	A	**Viet Nam**	M	D
Kuwait	VH	B	**Philippines**	M	C
Oman	VH	A	**Lao**	M	D
Qatar	VH	A	**Cambodia**	M	D
United Arab Emirates	VH	A	**Myanmar**	M	D
Australia	VH	A	**Nepal**	M	D
Brunei Dur	VH	B	**Indonesia**	M	C
Malaysia	VH	A	**India**	M	C
Singapore	VH	B	**Bangladesh**	M	D
Canada	VH	A	**Sudan**	L	D
USA	VH	A	**Palestine**	L	C
Albania	H	C	**Pakistan**	M	D
Azerbaijan	H	C	**Morocco**	M	C
Turkey	H	A	**Egypt**	M	C
Iran (Islamic Rep. of)	H	B	**Afghanistan**	L	D

HDI: Human Development index; VH: very high; H: high; M: medium; L: low. SF: serum ferritin; LIC: Liver iron concentration.

As previously stressed, the scoring and grading in Table 1(i) and Table 1(ii) indicate availability of basic services and not how effectively they are used. Availability is mainly related to the Human Development index (HDI).

According to this study:

- 5% of patients live in Very High HDI countries / territories.
- Poor or no availability of one or more iron chelating agents is reported in 9 / 31 countries / territories in the High to Low HDI group (29%).
- MRI availability and regular use of this monitoring tool are questionable for 10,983 (26%) patients living in Very High HDI countries / territories, 234,408 (69%) patients living in High HDI countries / territories and 100% of patients living in medium/low HDI countries / territories.
- Patient support for free chelation is offered in all but one country in the Very High HDI countries, based on universal health coverage. Singapore is the only country where health insurance is private and co-payment policy is the rule (including MRI for iron overload).
- Iron chelation is free in Iran, but only if locally produced agents are used. There is co-payment if original drugs are used.
- The generic iron chelators produced in Iran (Islamic Republic of), India, Turkey, other countries of the Eastern Mediterranean Region and elsewhere have not been adequately tested for effectiveness and safety. TIF receives concerns from patients regarding both these issues. This may have an impact on long-term iron chelation effectiveness and complication rates.

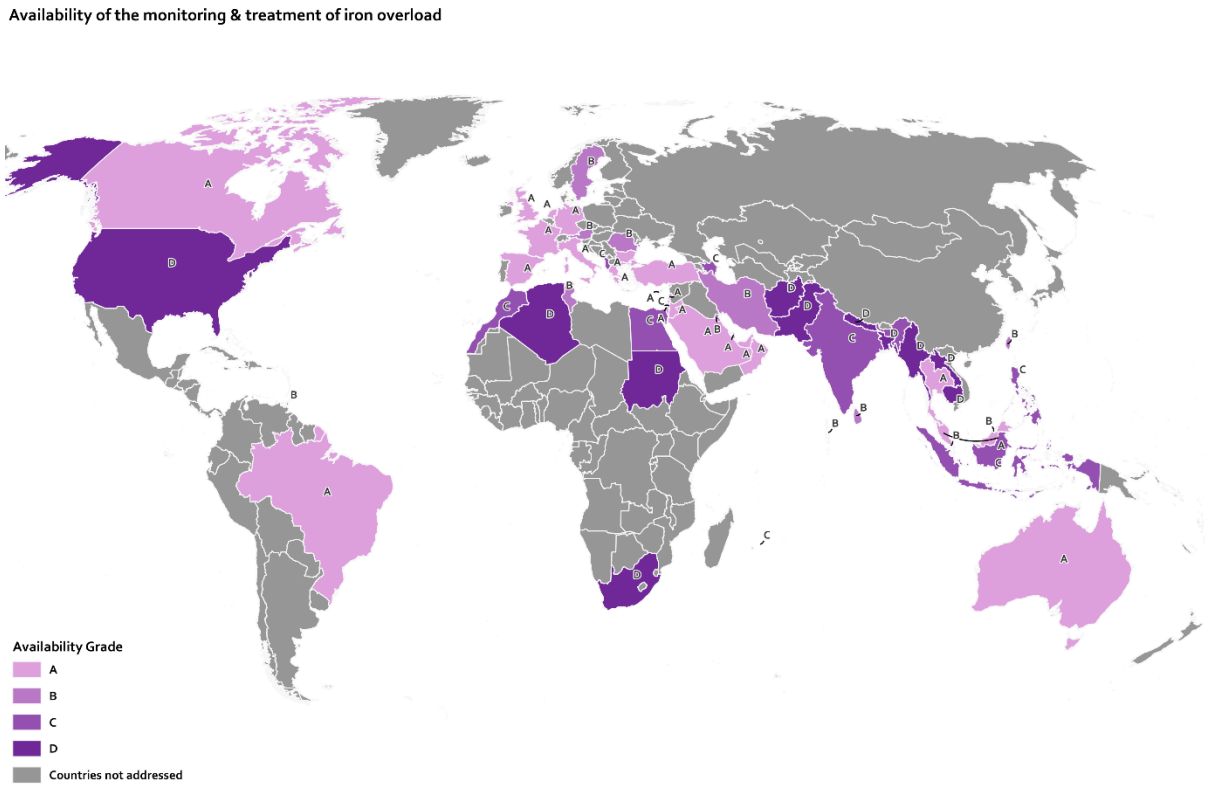

Figure 1. Map grading the availability of the monitoring/ treatment of iron overload across the globe (2024)

Effectiveness

As previously mentioned, beyond the availability of resources and services there is a further need to assess the effectiveness of iron overload control strategies since many factors mentioned earlier may lead to ineffective use of the agents, and thus impaired patient outcomes, in terms of morbidity, quality of life and mortality.

The first parameter examined was the mean age of patients, which is an indicator of success of total management but for which iron chelation is a major contributor. The countries / territories were divided according to the age of their patient population. Additional parameters included the range of serum ferritin levels, organ iron deposition (liver and heart) and most common medical complications including those of the heart and liver. Heart complications were considered to be reported as heart failure or arrhythmias. Liver complications were considered to be reported as fibrosis/cirrhosis, hepatic failure or hepatocellular carcinoma. An effort was made to collect all parameters from publications or other reports, such as TIF's delegation visits and presentations in TIF's regional and international conferences by local experts (see also analysis of patients' responses in an MRI specific survey held in October 2019 - in the 'Global review of MRI services for thalassaemia chapter). The corresponding scoring system used to grossly code these parameters is presented in Table 4.

Table 4. Scoring methodology to assess effectiveness of iron overload control (monitoring and measuring)

Mean Age (Years)	Score	Mean Serum Ferratin (NG/L)	Score	Mean Liver Iron Concentration (NG/G DW)	Score	Mean MRT T2* Heart (MS)	Score	Heart Complications (% Patients)	Score	Mean Liver Complications (% Patients)	Score
>30	12	<1000	6	<3	6		6	<10	6	<5	6
20-30	6	1-2000	3	3-7	3		3	11-20	3	6-10	3
15-20	2	2-3000	1	7-15	1		1	21-30	1	10-20	1
<15	0	>3000	0	>15	0		0	>30	0	>20	0

Based on the above scoring methodology, countries were graded A – D (Table 3) according to their accumulated score, as explained in Table 4 and presented in Table 3 (under the title "Effectiveness").

Table 5. Grading based on Table 4 scoring

Score	Grade
30-42	A
20-30	B
10-20	C
<10	D

A very important limitation to this approach was the paucity of evidence, since not all countries / territories collect national data; in fact, very few centres keep a registry to collect reliable information on all their patients. In addition, not all countries / territories have MRI results and even fewer report MRI results. It was thus to-date not possible to grade the majority of the countries / territories with respect to the effectiveness of their iron overload control policies. Such scoring, and despite being grossly calculated, demonstrates that countries / territories with a mean age of their patient population >30 years are most likely to score **A** and **B** in addressing effectively or quite effectively iron monitoring and chelation treatment. Scoring of **A** or **B** however was only possible to be reported for very few countries including Cyprus, Italy, Greece and the United Kingdom

where results of the relevant parameters shown in Table 4 were available through published literature. For a number of other countries only the age distribution was made available either in published data or through official TIF's reports, and in their greatest majority a mean age of less than or around 20 years of age was reported i.e. grade **C** or **D** (as shown in Table 6 below and maps **A** and **B** at the end of this chapter) parallel to the grading of the services' availability. It is evident that almost every country that scores **A** or **B** in service availability demonstrates levels **A** or **B** effectiveness of iron monitoring and treatment as well.

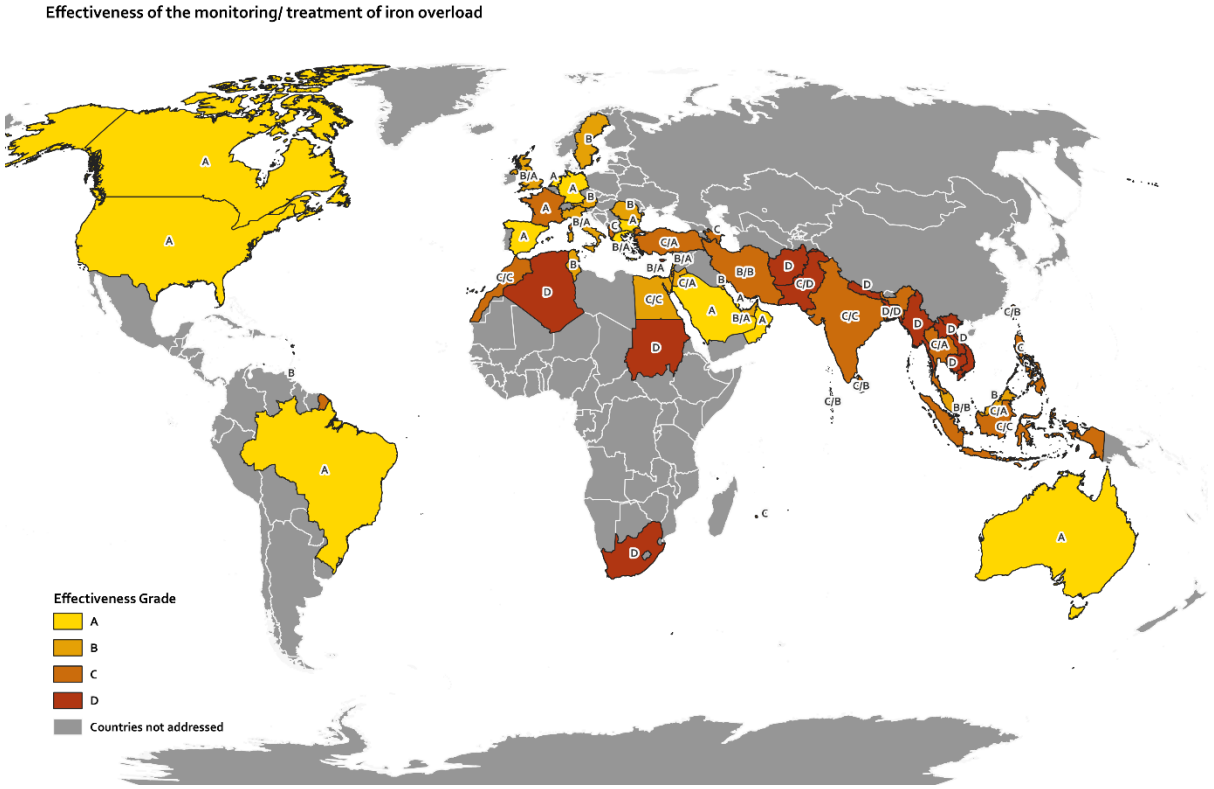

Figure 2. Map grading the effectiveness of the monitoring/ treatment of iron overload across the globe

Table 6. Availability and effectiveness of the monitoring for and treatment of iron overload

Country	HDI	Grading Effectiveness	Availability	Country	HDI	Grading Effectiveness	Availability
Austria	VH		B	**Jordan**	H	C	A
Bulgaria	VH		A	**Lebanon**	H	B	A
Cyprus	VH	B	A	**Tunisia**	H		B
France	VH		A	**Maldives**	H	C	B
Germany	VH		A	**Sri Lanka**	H	C	B
Greece	VH	B	A	**Thailand**	H	C	A
Israel	VH		A	**China**	H		D
Italy	VH	B	A	**Taiwan, China**	VH	C	B
Netherlands	VH		A	**Brazil**	H		A
Romania	VH		B	**Trinidad & Tobago**	H		B
Spain	VH		A	**Mauritius**	H		C

Country	HDI	Grading Effectiveness	Availability	Country	HDI	Grading Effectiveness	Availability
United Kingdom	VH	B	A	**Algeria**	H		D
Sweden	VH		B	**South Africa**	M		D
Saudi Arabia	VH		A	**Viet Nam**	M		D
Kuwait	VH		B	**Philippines**	M		C
Oman	VH		A	**Lao**	M		D
Qatar	VH		A	**Cambodia**	M		D
United Arab Emirates	VH	B	A	**Myanmar**	M		D
Australia	VH		A	**Nepal**	M		D
Brunei Dur	VH		B	**Indonesia**	M	C	C
Malaysia	VH	C	A	**India**	M	C	C
Singapore	VH	B	B	**Bangladesh**	M	D	D
Canada	VH		A	**Sudan**	L		D
USA	VH		A	**Palestine**	L	C	C
Albania	H		C	**Pakistan**	M	C	D
Azerbaijan	H		C	**Morocco**	M	C	C
Turkey	H	C	A	**Egypt**	M	C	C
Iran (Islamic Rep. of)	H	B	B	**Afghanistan**	L		D

HDI: Human Development index; VH: very high; H: high; M: medium; L: low. SF: serum ferritin; LIC: Liver iron concentration.

Patient Adherence

Apart from non-availability of the means to control iron overload, poor adherence to treatment remains a major factor affecting iron related morbidity and mortality. Adherence is defined by the World Health Organization (WHO) as "*the extent to which a person's behaviour in taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a healthcare provider*" [65].

There is no gold-standard method for measuring adherence and thus a variety of strategies have been reported [66, 67, 68]. In general, adherence is assessed using either a process-oriented or an outcome-oriented definition. In the process-oriented definition, patient behaviour is evaluated either by self-reporting [69] or by objective measures, such as pill counting. Patients are asked to rate their adherence behaviour either by asking direct questions or by using standardized patient questionnaires. Overall, the self-rating of adherence usually results in its overestimation. Some more objective approaches to assess adherence using the process-oriented definition include measuring the remaining dosage units during visits or using electronic monitoring devices (medication event monitoring systems) which record the date and time when a medication container is opened. In the outcome-oriented definition, an estimate of treatment outcome, usually a biochemical measurement (e.g. blood sugar or serum ferritin), is used to mirror the outcome of treatment. This approach may also be misleading as tests may be influenced by several additional factors such as diet, absorption or excretion rate, concomitant medications or interventions or comorbidities. In summary, measuring and reporting adherence levels is never an accurate process, but still, despite pitfalls, a necessary indicator of the results of iron overload management.

Adherence to iron chelation therapy is of key importance to maintain iron balance and prevent iron accumulation in the liver, heart, and endocrine glands. Continuous protection from the toxic labile iron requires compliance with a regular iron chelation regimen and not intermittent high-dose chelation boosts. Lack of compliance is followed by higher rates of cardiac and endocrine complications, and lower overall survival as well as higher disease-related healthcare expenditure [70, 71].

In this report, TIF has relied on published information on patient adherence. The reported adherence to iron chelation therapy varies widely by time period, region and chelation regimen. A summary of the main publications is listed in Table 7.

Table 7. Main studies reporting thalassaemia patients' adherence to iron chelation therapy

Study	Year	Country	No. of Patients	Method	Drug	Adherence Level
ARBORETTI R ET AL. EUR J CLIN PHARMACOL	2001	Italy	867	Interviews, self-reporting	DFO	
AYDINOK Y ET AL. PAEDIATR INT	2005	Turkey	38	Self-reported	DFO	
PAQBAZ Z ET AL. ANN NY ACAD SCI	2005	USA	90	Self-reported	DFO	
TRACHTENBERG F ET AL. AM J HEMATOL	2011	USA, United Kingdom	97	Self-reported	DFO/DFX	
PORTER J ET AL. ANEMIA	2012	Australia, Belgium, France, Germany, Greece, Italy, United Kingdom, Netherlands	274	SICT questionnaire Changing ICT to DFX	DFX	
TRACHTENBERG F ET AL. QUAL LIFE RES	2014	USA, United Kingdom, Canada	391	Self-reported	DFO/DFX/DFP	
HATZIPANDELIS ES ET AL. HEMOGLOBIN	2014	Greece	36	Self-reported	Combination DFO/DFP	
AL-KOUB MI ET AL. PEDIATR HEMATOL ONCOL	2014	Jordan	164 (aged 12-19)	Interview	DFX	
HAGHPANAH S. HEMATOL	2014	Iran	220	Self-reported	DFO 114 pts DFX 106 pts	
VEKEMAN F ET AL. J MED ECON	2016	USA	218 (TM)	Medication possession ratio (MPR)	DFO/DFX/DFP	
ZEYDI AE ET AL. ELECTRON PHYSICIAN	2017	Iran	18	Semi-structured interview	All 3 chelators	

Study	Year	Country	No. of Patients	Method	Drug	Adherence Level
TAHER A ET AL. AM J HEMATOL	2017	Lebanon, Greece, United Kingdom, etc.	173	Self-reported PROs	DFX	
CHENG WY ET AL. CURR MED RES OPIN	2018	USA	348 (TM)	Medication possession ration (MPR)	DFX	
SIDHU S ET AL IJHOSCR	2020	India	215 (TM mean age 15 years)	Questionnaire, self-reported	All 3 chelators	
THEPPORNPITAKK ET AL	2021	Thailand	70	MMAS-8	All 3 chelators	

The reported results are variable and derived by different methodologies. However, they indicate a less than optimum usage of a treatment whose neglect may have serious long-term consequences. One aspect not often detected by studies, such as those exemplified above, is the fact that many patients experience periodic or episodic lapses in their adherence. This behaviour may be associated with situational psychological factors [86], but also other events such as travelling. These episodes will allow free iron to damage cells even though this may not be detected by simple monitoring with serum ferritin.

Causes And Management of Non-Adherence

The lack of adherence to therapy does not merely imply the failure of a patient to comply with the prescribed medications or to attend the scheduled visits or assessments. It is a rather complicated and multi-factorial issue; the causes of which may be related to the organization of healthcare provision, the knowledge and skills of treating physicians, the complexity and safety of therapeutic modalities and certainly the attitude of patients and their social environment towards their illness and its therapy. Table 6 summarizes the potential sources of non-adherence in patients with thalassaemia.

An established and well-running national or regional thalassaemia management programme designed and implemented by the corresponding health authorities is of key importance. In this context, the allocation of sufficient healthcare resources, including the financial coverage of related therapies and the development of dedicated thalassaemia centres constitute strategic components of a successful thalassaemia management plan.

The treating physicians and nurses play a crucial role for the adherence of patients to the indicated therapies. **Two important barriers to patient adherence are the non-adherence of physicians to guideline recommendations and the failure to develop an adequate approach to patients and to establish a collaborative relationship with them.** A common denominator for those barriers is often the lack of proper education and training of physicians on updated clinical practice guidelines and on a paternalistic approach to patients with chronic diseases.

These elements of patient care, well organised services, financial support and, perhaps above all, the quality of the professional/patient relationship and psychosocial support, will result in patient satisfaction, which has been linked to adherence [87,88]. Therapeutic regimens are often difficult to adhere to, particularly in the case of composite multi-systemic diseases such as thalassaemia; and the lifelong duration of therapy, the possible

side effects that may compromise the quality of life as well as the frequent hospital visits that interfere with the professional, and social life of patients constitute additional barriers to adherence [89].

Often patients do not have sufficient knowledge of their disease and its therapeutic requirements. **Better disease knowledge has actually been shown to correlate positively with adherence to therapy by different studies** [90] even though one study from Malaysia found no association between the adherence level and knowledge on thalassemia, while low family income was more likely to associated with poor adherence [91]. The issue of supervision and overall family support is also important, avoiding overprotectiveness. Social support is important; however, schoolteachers or work colleagues and supervisors are often unaware of patients' condition and therefore unable to be supportive [92]. Furthermore, financial constraints may represent important barriers when full financial coverage of therapies and assessment is not provided by the healthcare system. Stigmatisation and social isolation may have significant adverse effects on patients' compliance, while the presence of psychological distress or even illness may further be an important reason of non-adherence. The transition of care from one institution to another or from paediatric to adult care is often hurried and not well prepared and may lead to a violent disruption of the patient-physician relationship as the patient may feel uncomfortable in the new facility and may not trust the new medical personnel. Finally, cultural or religious issues may further intervene if not properly discussed and addressed by treating physicians.

A strategy to improve adherence to therapy in TDT patients should first investigate all the aforementioned potential sources of barriers and then develop measures to address each one of them. Table 8 outlines a list of actions that may address the different sources of non-adherence in patients with TDT, along with the corresponding stakeholders that those actions should target.

The provision of effective and safe pharmaceutical products is of utmost importance for patients' compliance. This has become an issue in some countries where substandard generics are provided as a means to reduce costs, but with increased adverse effects. On the other hand, comparisons of adherence to different chelating agents in the course of clinical trials give higher than average adherence rates due to participants following a specific programme for a relatively short period of time.

There are many interventions that may limit patient-related lack of compliance. The institution of simple things, such as alarms or reminder systems may address forgetfulness and negligence. Patients should be encouraged to express their concerns about therapy and participate in the scheduling of regimens visits and assessments to best fit their school, work, family, and social activities. Children and adolescents mainly, but also older and severely ill patients should be supervised and supported with as much discretion and expertise as possible by family members.

Table 8. Causes of non-adherence to therapy in patients with thalassaemia and suggested interventions to overcome them.

Causes of non-adherence	Stakeholders	Suggested Interventions
Healthcare-Related		
1. Lack of healthcare resources 2. Lack or inadequate thalassaemia management programmes 3. Lack of financial coverage 4. Lack of specialized centres	1. Healthcare authorities 2. Patient and parent associations 3. Pharmaceutical industry 4. Academia 5. International health organizations / bodies	1. Development of national/regional thalassaemia management programmes 2. Provision of financial coverage for disease-related healthcare expenditures, reducing out-of-pocket expenses 3. Development of dedicated centres for the management of patients with haemoglobinopathies (v. Reference Centres – for more information see relevant Chapter) 4. Widespread use of effective and safe generic drugs
PHYSICIAN-RELATED		
1. Non-adherence to clinical practice guideline recommendations / standards of care 2. Inadequate approach to patients	1. Treating physicians 2. Health authorities 3. Medical administration 4. Medical associations 5. Academia	Education and training on current clinical practice recommendations Assessment and documentation of compliance with medical prescriptions and instructions Development of a relationship of mutual trust with patients ; an active role of the patient and a collaboration with the physician Understanding of patients' concerns about therapy and response to them Arrangement of regimens and visits according to patients' professional, family and lifestyle needs

TREATMENT-RELATED		
• Complexity of regimens • Duration of regimens • Schedules contrasting patients' lifestyle • Physical and emotional distress • Side effects	• Drug regulatory authorities • Pharmaceutical industry • Healthcare authorities • Treating physicians	• Improvement of drug safety • Improvement of delivery systems • Decrease complexity of regimens • Comprehensive education of patients on how to avoid treatment-related distress and side effects • Limitation and effective management of side effects • Arrangement of regimens and visits to fit patients' school, work, family, and social needs
PATIENT-RELATED		
• Lack of understanding • Forgetfulness and negligence • Lack of supervision • Poor family and social support • Severity of medical condition • Financial issues • Stigma and social isolation • Psychiatric illness • Inappropriate transition of care • Cultural or religious issues	• Patients • Parents and family • Treating physicians • School teachers • Social and community groups • Patient associations	• Reminders and alarms, (e.g. through mobile apps such as TIF's THALIA Mobile App) • Family supervision for children, adolescents, but also older and severely ill • Family education • Psychological support and therapy aiming for a self- motivated decision to adhere to the advice of the doctor. Cognitive behavioural therapies • Support by social workers • Engagement in sports, hobbies, and social activities • Well prepared transition of care

Safety concerns, both acute and long-term, are important with iron chelating agents just as in any other medications. As the thalassaemia patient population ages more long-term effects are becoming apparent and physicians should be alert to the possibility and be ready find solutions for each affected individual. One major example is the effect on ocular function which seems to be more frequent with the long term use of desferrioxamine [93] [Nuzzi R, Geronazzo G, Tridico F, Nuzzi A, Caselgrandi P, Piga AG. Long-Term Effects of Iron Chelating Agents on Ocular Function in Patients with Thalassemia Major. Clin Ophthalmol. 2021 May 20; 15:2099-2109. doi: 10.2147/OPTH.S300974. PMID: 34045846].

CONCLUSIONS

The lack of adherence to therapy remains a significant unmet need in the management of patients with thalassaemia. It may substantially compromise the beneficial effects of modern therapy to patient prognosis and quality of life. It is a multi-factorial problem originating from several different sources, including issues related to healthcare system, treating physicians, therapeutic regimens, patients, family and social environment. The evaluation of patients' compliance with the prescribed medications, scheduled visits and assessments should be part of regular process with relevant recording and investigation to improve adherence levels. All potential sources of non-adherence should be addressed by the involvement of healthcare authorities, academia, medical associations, treating physicians and other specialists, pharmaceutical industry, family, social groups, and patient associations.

TIF has, for some time now, undertaken a series of initiatives to promote awareness on the importance of adherence of all stakeholders and interventions that may improve it. To this end, TIF acts in close collaboration with government officials, healthcare authorities and policymakers, medical associations, and healthcare professionals as well as thalassaemia patient and parent organizations. TIF works to form active, knowledgeable, and empowered thalassaemia patients who, with joint actions with relevant stakeholders, will promote the availability and effectiveness of iron load monitoring and iron chelation treatment effectiveness. Appropriate iron load management constitutes the second major pillar after blood transfusion therapy that contributes to the successful management of a multiorgan, chronic disease such as thalassaemia. It is clear from the compiled information and gross grading of the availability and effectiveness of iron load monitoring and treatment presented in this chapter (please see also maps A and B at the end of this chapter), that considerable works needs to be undertaken in the majority of the countries where this disorder is of medium to high prevalence. Huge gaps and extensive heterogeneity are observed in this area within and across counties which underscores the huge inequalities across the world with regards to equal rights of patients for quality heath and other care. Through the sensitization and provision of reliable and patient-oriented information to healthcare authorities and planners, as part of their advocacy efforts, the patients and their families have a very crucial role to play. In addition, TIF also aims at the continuous improvement of the efficacy and safety of pharmaceutical products and devices associated with the care and treatment of thalassaemia in close collaboration with the WHO its patient associations members, the academia, the industry and national, regional and international medical, scientific and regulatory bodies.

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