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Review

The Interplay Between β-Thalassemia and the Human Virome: Immune Dysregulation, Viral Reactivation, and Clinical Implications

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Abstract

β-thalassemia is a chronic genetic blood disorder characterized by defective β-globin synthesis, requiring frequent transfusions and resulting in iron overload, immune dysfunction, and increased susceptibility to infections. In these immunocompromised patients, altered immune responses lead to significant changes in the human virome, promoting viral persistence, reactivation, and expansion of pathogenic viral communities. This review explores the intricate relationship between β-thalassemia and the human virome, focusing on how clinical interventions and immune abnormalities reshape viral dynamics, persistence, and pathogenicity. Patients with β-thalassemia exhibit profound innate and adaptive immune dysregulation, including neutrophil dysfunction, T cell senescence, impaired B cell and NK cell activity, and expansion of myeloid-derived suppressor cells. These alterations create an immunological niche that favors viral reactivation and virome expansion. Iron overload enhances viral replication, while chronic transfusions introduce transfusion-transmitted viruses. Splenectomy and allo-HSCT further compromise viral surveillance. Additionally, disruptions in the gut virome, particularly bacteriophage-driven dysbiosis, may exacerbate inflammation and impair host–virus homeostasis. The human virome is not a passive bystander but a dynamic player in the pathophysiology of β-thalassemia. Understanding virome–immune interactions may offer novel insights for infection monitoring, risk stratification, and precision therapies in thalassemic patients.

Keywords: β-thalassemia; human virome; immune dysregulation; viral reactivation; iron overload; transfusion-transmitted infections; neutrophil dysfunction; lymphocyte impairment

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1. Introduction

β-thalassemia is one of the most prevalent hereditary blood disorders worldwide, characterized by mutations in the *HBB* gene of chromosome 11 that lead to reduced or absent β-globin chain synthesis, resulting in severe anemia and related complications [1]. β-thalassemia has been described primarily as an autosomal recessive disorder. β-thalassemic individuals are typically classified into three clinical categories: β-thalassemia major (β-TM; the most severe form, characterized by early-onset transfusion-dependent anemia), β-thalassemia intermedia (β-TI; a moderate form with variable severity that may or may not require occasional transfusions), and β-thalassemia minor (carrier; usually asymptomatic

or presenting with mild microcytic anemia) [2]. With over 300 known β-thalassemia mutations, this disorder is prevalent in regions historically affected by malaria, including the Mediterranean, Middle East, and South Asia [3]. An estimated 60,000–70,000 children are born annually worldwide with β-thalassemia with more than half of them reported to require regular blood transfusions [4]. Other therapeutic approaches include iron chelation therapies, fetal hemoglobin upregulation, etc., to alleviate disease symptoms, as well as other clinical approaches, like hematopoietic stem cell transplantation, etc., to resolve the disease pathology [5–7]. These interventions alongside iron overload, chronic inflammation, and frequent hospital exposure lead to dysfunction of various organs.

The human body harbors an extensive collection of viruses known as the human virome, encompassing both pathogenic and commensal viruses that coexist within various niches, including the gut, respiratory tract, skin, and blood [8]. The human virome plays an essential role in shaping immunity, influencing disease susceptibility, and modulating the outcomes of chronic illnesses, particularly in individuals with underlying genetic or immunological conditions. In individuals with immunocompromised states such as β-thalassemia patients, the balance of the virome can shift, leading to reactivation of latent viruses or altered viral dynamics, contributing to disease pathogenesis or exacerbation of existing conditions [8,9]. The intricate interaction between the human virome and β-thalassemia pathophysiology has garnered increasing attention. For instance, chronic viral exposure can alter inflammatory cytokine profiles and modulate host gene expression, potentially affecting erythropoiesis and immune cell maturation. Conversely, iron overload, common in β-thalassemia patients, creates an environment conducive to viral replication, influencing viral persistence and reactivation [10]. Additionally, the use of iron chelators and immunomodulatory agents may further shape the viral landscape in these individuals.

This review aims to explore the interplay between beta-thalassemia and the human virome, with a particular emphasis on how various pathogenic mechanisms, such as chronic transfusions, iron overload, immune dysregulation, and clinical implications, collectively reshape viral composition, reactivation potential, and overall virome dynamics. By examining these disease-driven alterations, the review seeks to provide insight into the evolving landscape of the human virome in thalassemic individuals and its potential implications for disease progression and immune homeostasis. Therefore, after outlining virome–host interactions, we focus on how beta-thalassemia's unique pathophysiology provides a conducive environment for virome alterations, despite limited direct virome studies to date.

2. Methods for Literature Review

This review was narrative in nature. Literature searches were conducted using PubMed and Google Scholar up to July 2025, covering the period from 2000 to 2025. The following keywords and MeSH terms were used: "beta-thalassemia", "human virome", and "blood virome" OR "immune dysregulation" OR "virus reactivation" OR "blood transfusion". Approximately 200 publications were retrieved and assessed for relevance. Duplicates and studies containing pre-existing data were excluded. Only articles published in English were considered. Reference lists of the selected articles were also screened to identify additional relevant studies. The selected articles were divided between the two authors for detailed analysis and summarization. Non-pertinent papers were excluded, and the extracted data were subsequently discussed and synthesized collaboratively.

3. Composition of Human Virome

Recent studies have demonstrated that the human virome varies significantly across different anatomical sites. It consists of bacteriophages, eukaryotic viruses, and endogenous retroviruses, each contributing uniquely to host-microbe interactions and immune modulation (Figure 1) [11,12]. Bacteriophages are widely distributed, and their composition differs by site, largely reflecting the diversity of local bacterial communities. Similarly, the distribution of eukaryotic viruses is site-specific, influenced by tissue tropism and host immune status. Virome components have been detected in multiple biological compartments, including the gut, skin, oral cavity, blood, feces, and cerebrospinal fluid, emphasizing their pervasive presence and potential systemic impact (Table 1).

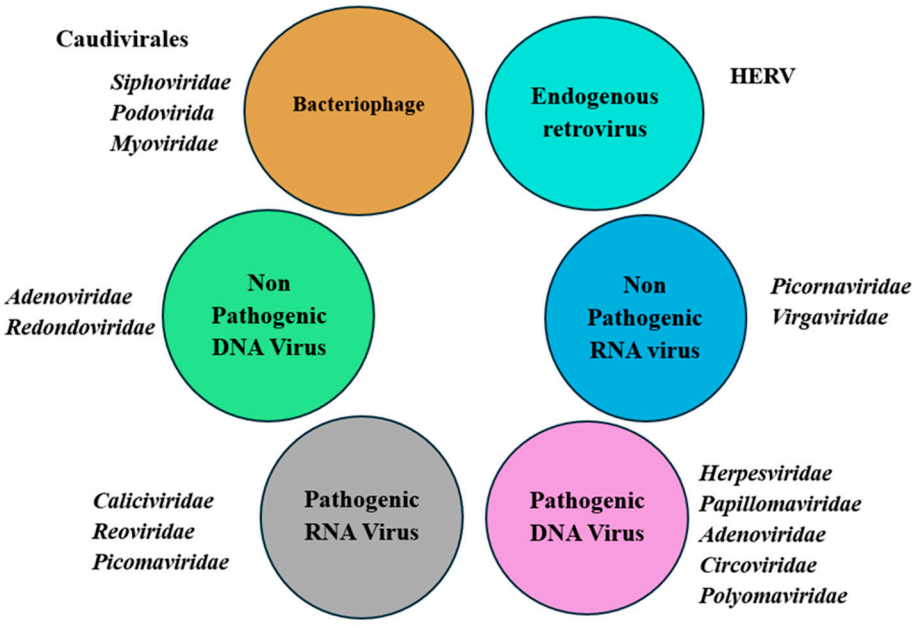


Figure 1. Different viruses in human virome. Bacteriophages, eukaryotic RNA viruses, eukaryotic DNA viruses, and endogenous retroviruses colonize the human body [8].

Table 1. The human virome at different body sites of the body. Summary of viruses, and bacteriophages found at each human body site [13].

Different Body Part	Virome Group	Example	Phage Group	Example
Central Nervous System	*Herpesviruses*	HSV-1, HSV-2	*Siphoviridae*	λ phage, *Streptococcus* phage φC1
			Podoviridae	T7 phage, *Bacillus* phage φ29
	Polyomaviruses	JC virus, BK virus	*Myoviridae*	T4 phage, *Pseudomonas* phage PB1
Eyes	*Herpesviruses*	HSV-1	*Siphoviridae*	λ phage, *Streptococcus* phage φC1
	Adenoviruses	Adenovirus serotype 8,	*Podoviridae*	T4 phage, *Pseudomonas* phage PB1
			Myoviridae	λ phage, *Streptococcus* phage φC1
	Papillomaviruses	HIV-16	*Microviridae*	φX174
Oral/Nasal Cavity	*Anelloviruses*	Torque teno virus (TTV),	*Siphoviridae*	λ phage, *Streptococcus* phage φC1
	Herpesviruses	EBV, HSV-1	*Myoviridae*	T4 phage, *Pseudomonas* phage PB1
	Papillomaviruses	HPV	*Leviviridae*	MS2

Table 1. *Cont.*

Different Body Part	Virome Group	Example	Phage Group	Example
Lungs	*Anelloviruses*	TTV	*Podoviridae*	T7 phage, *Bacillus* phage φ29
	Paramyxoviruses	RSV, HMPV	*Myoviridae*	T4 phage, *Pseudomonas* phage PB1
	Influenza viruses	Influenza A		
Gastrointestinal Tract	*Enteric viruses*	Norovirus, Rotavirus, Astrovirus	*Siphoviridae*	λ phage, *Streptococcus* phage φC1
			Podoviridae	T7 phage, *Bacillus* phage φ29
			Myoviridae	T4 phage, *Pseudomonas* phage PB1
	Anelloviruses	TTV	*Microviridae*	φX174
	Adenoviruses	Adenovirus 41	*Inoviridae*	M13 phage
			Leviviridae	MS2
Skin	*Papillomaviruses*	HPV-1, HPV-8	*Siphoviridae*	λ phage, *Streptococcus* phage φC1
	Polyomaviruses	Merkel cell polyomavirus, TTV	*Myoviridae*	T4 phage, *Pseudomonas* phage PB1
			Inoviridae	M13 phage
Blood (Plasma)	*Anelloviruses*	TTV	*Siphoviridae*	λ phage, *Streptococcus* phage φC1
			Podoviridae	T7 phage, *Bacillus* phage φ29
	Herpesviruses	CMV, EBV	*Myoviridae*	T4 phage, *Pseudomonas* phage PB1
	Retroviruses	HIV	*Microviridae*	φX174
	Polyomaviruses	BK virus	*Inoviridae*	M13 phage
Genitourinary Tract	*Herpesviruses*	HSV-2, CMV	*Siphoviridae*	λ phage, *Streptococcus* phage φC1
	Papillomaviruses	HPV-16, HPV-18	*Podoviridae*	T7 phage, *Bacillus* phage φ29
	Polyomaviruses	JC virus	*Microviridae*	φX174
Urine	*Polyomaviruses*	BK virus, JC virus	*Siphoviridae*	λ phage, *Streptococcus* phage φC1
	Anelloviruses	TTV	*Podoviridae*	T7 phage, *Bacillus* phage φ29
			Myoviridae	T4 phage, *Pseudomonas* phage PB1

4. Neutrophil-Associated Immune Dysregulation in β-Thalassemia: Implications for Human Virome Alterations

In β-thalassemia, the innate immune system particularly neutrophil function is profoundly impaired, contributing to increased susceptibility to infections [14]. Neutrophils of thalassemic patients display considerably decreased functional activity compared to those isolated from healthy controls [15]. The exact reasons for the failure of neutrophils to mount appropriate responses remain indefinite [16]. Neutrophils in thalassemic patients exhibit significant defects in migration, chemotaxis, phagocytosis, and oxidative microbial killing [14]. One major disruption involves the CXCR2–CXCL2 chemokine axis, where reduced CXCR2 expression leads to impaired recruitment of neutrophils to sites of infection, especially under bacterial challenge [14]. Furthermore, surface receptor abnormalities including diminished expression of CD11b (a subunit of complement receptor 3) and altered levels of CD16, CD18, CD45, TLR4, and CD32 interfere with effective pathogen recognition and clearance [14,17–20]. These functional impairments are accompanied by elevated

oxidative stress, characterized by increased membrane lipid peroxidation and reduced glutathione levels, likely due to iron overload and chronic inflammation. Although basal levels of reactive oxygen species are often high, neutrophils show reduced capacity for inducible ROS generation due to dysregulation of NADPH oxidase components such as p47phox, p40phox, gp91phox, and p22phox, leading to compromised respiratory burst and bactericidal activity [19]. Morphologically, neutrophils from thalassemic patients often appear hypo-segmented and immature, with an increased proportion of band cells in circulation, indicating defective maturation. This arrested development is linked to downregulation of the transcription factor PU.1, which governs critical functions including phagocytosis, oxidative burst, granulocyte colony-stimulating factor receptor (G-CSFR) signaling, and apoptotic regulation [21,22]. Reduced PU.1 expression correlates with poor neutrophil functionality and has been observed in both murine thalassemia models and human patients, particularly those with severe diseases [23]. Additionally, evidence suggests abnormalities in apoptotic pathways, with some studies reporting increased expression of caspases, while others suggest extended survival of dysfunctional neutrophils. These cumulative defects in neutrophil biology spanning impaired chemotaxis, phagocytosis, ROS generation, and maturation create a permissive environment for recurrent, often severe bacterial infections in individuals with β-thalassemia.

While the pivotal role of neutrophils in defending against bacterial pathogens is well established, their involvement in antiviral immunity and virome regulation remains comparatively underexplored. Upon bacterial infection, local resident macrophage and mast cells secrete cytokines, such as tumor necrosis factor (TNF) and interleukin (IL)-1β, which activate endothelial cells to capture circulating neutrophils [24]. Neutrophils also play a multifaceted role in antiviral immunity, exhibiting both protective and potentially detrimental effects during viral infections. Following infection with highly pathogenic viruses such as influenza and herpes simplex virus (HSV), the recruitment of neutrophils into the lungs and airways contributes significantly to disease resolution by limiting viral replication and dissemination [25]. One of the key antiviral mechanisms involves the secretion of pentraxin 3 (PTX3), a soluble pattern recognition molecule. Both human and murine studies have shown that PTX3 binds to influenza virus and mediates antiviral effects such as inhibition of hemagglutination, neutralization of viral infectivity, and inhibition of neuraminidase activity [26]. Moreover, neutrophils contribute to antiviral defense through the formation of neutrophil extracellular traps (NETs), which can entrap and neutralize viral particles, a mechanism that may be compromised in β-thalassemia [27].

Neutrophil granules contain a range of antimicrobial effectors, including myeloperoxidase (MPO), defensins, and cathelicidins, all of which exhibit antiviral activity. Specifically, defensins are capable of directly binding to viral particles by interacting with the lipid bilayers, glycoproteins, and glycolipids of viruses such as HIV-1 and HSV [28,29]. Additionally, several viruses including HIV, hepatitis B and C viruses, rhinovirus, HSV-1, RSV, and influenza, can stimulate neutrophils to produce ROS [29,30]. These ROS have virucidal properties, enabling direct damage to viral nucleic acids and promoting apoptosis of virus-infected cells, thereby limiting viral dissemination [31,32].

In the context of β-thalassemia, a marked reduction in neutrophil number and function, within local tissue microenvironments may compromise frontline immune defenses, thereby creating a permissive niche for viral persistence, reactivation, or opportunistic infection. This immunological gap not only heightens susceptibility to viral pathogens but may also drive shifts in the composition and behavior of the human virome, potentially contributing to disease progression and systemic immune dysregulation. The dysregulated neutrophil responses observed in various viral infections such as excessive recruitment, heightened production of proinflammatory mediators, and subsequent tissue damage [33] closely

resemble the neutrophil dysfunction seen in beta thalassemia [34]. Moreover, a growing body of research indicates that viruses can exploit neutrophils as vehicles for dissemination. For example, West Nile virus (WNV) not only hijacks neutrophils for systemic transport but also replicates within them, enhancing viral spread within the host [35]. Similarly, horizontal transmission of sexually transmitted viruses such as HIV, herpesviruses, and papillomaviruses via sperm cells is well documented, and a potential role for spermatozoa in vertical transmission has also been proposed [36]. These findings collectively highlight the dual nature of neutrophil-virus interactions, while neutrophils possess potent antiviral mechanisms, they can also be subverted by viruses, adding complexity to the host's immune response (Figure 2) [25,26].

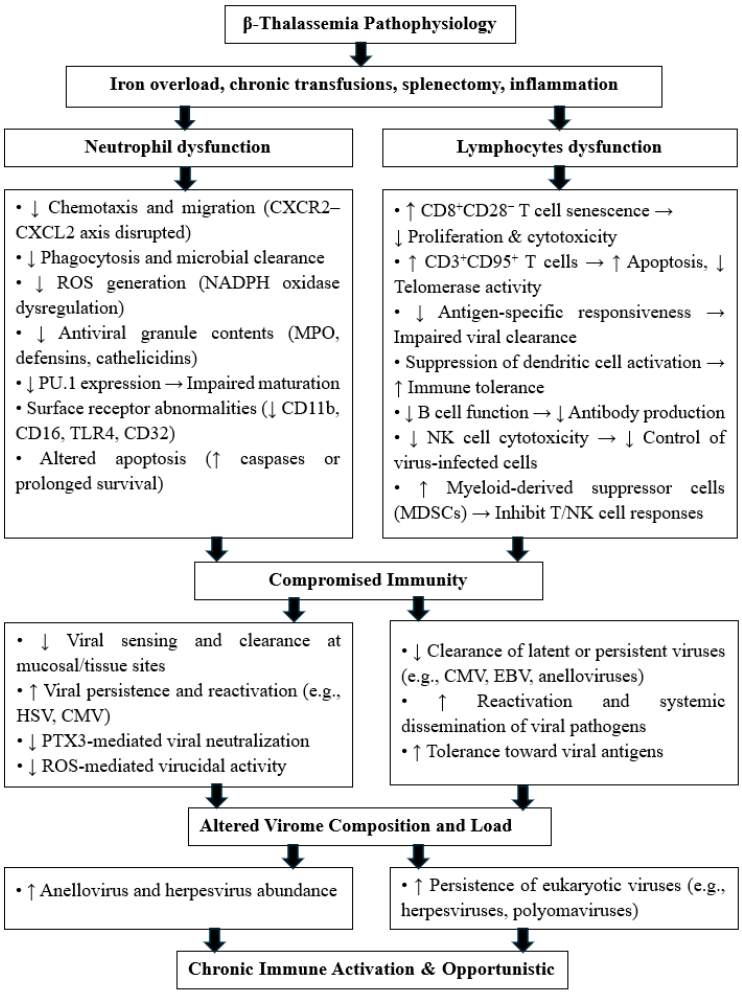


Figure 2. Immune Cell–Mediated Modulation of the Human Virome in β-Thalassemia. In β-thalassemia, both innate and adaptive immune dysfunctions contribute to alterations in the human virome. Neutrophils exhibit impaired chemotaxis, phagocytosis, oxidative burst, and antiviral effector functions due to iron overload, chronic inflammation, and defective maturation. These defects compromise frontline antiviral defense and create a permissive environment for viral persistence and reactivation. Simultaneously, profound lymphocyte dysregulation marked by $CD8^+$ T cell senescence, diminished B and NK cell activity, and expansion of immunosuppressive myeloid-derived suppressor cells (MDSCs) further weakens viral clearance and promotes immune tolerance. The cumulative result is increased virome diversity and abundance, especially of persistent viruses such as herpesviruses, anelloviruses, and polyomaviruses. Additionally, impaired recognition and response to bacteriophages via TLR-mediated pathways and increased microbial translocation from the gut may intensify cross-kingdom interactions. Together, these disruptions in immune surveillance reshape the virome and contribute to systemic immune dysregulation and susceptibility to opportunistic infections in β-thalassemia patients. "↑" indicates increasing, "↓" indicates decreasing.

5. Lymphocytes (T Cell, B Cell, NK Cells)-Associated Immune Dysregulation in β-Thalassemia: Implications for Human Virome Alterations

In patients with β-thalassemia, profound immune dysregulation, including T-cell senescence, impaired B cell and NK cell function, and expansion of immunosuppressive myeloid cells creates a permissive environment for viral persistence, reactivation, and altered virome dynamics [18,37,38]. Senescent $CD8^+CD28^-$ T cells with reduced proliferative capacity and compromised antigen responsiveness, alongside increased $CD3^+CD95^+$ populations and diminished telomerase activity, impair cytotoxic responses and weaken adaptive immunity. These dysfunctional T cells not only fail to clear viral infections efficiently but also suppress dendritic cell activation, promoting immune tolerance [39]. Similarly, the expansion of myeloid-derived suppressor cells (MDSCs) in peripheral organs further suppresses T-cell and NK cell-mediated antiviral defenses [40]. Emerging evidence also highlights that immune cells such as dendritic cells, B cells, and monocytes can internalize bacteriophages and respond via TLR-mediated pathways, including TLR3 and TLR9, triggering production of type I interferons, IL-6, IL-10, IL-12, and IFN-γ [41]. These innate responses are known to influence viral replication, latency, and clearance. Furthermore, interactions between bacteriophages, gut bacteria, and eukaryotic viruses such as lipopolysaccharide-mediated stabilization of poliovirus or TLR4-driven IL-10 induction by mouse mammary tumor virus, demonstrate how microbial and immune landscapes shape virome behavior [13]. In thalassemia, where immune surveillance is compromised and microbial translocation may be more likely due to chronic inflammation and splenic dysfunction, such trans-kingdom interactions may be intensified. Additionally, dysregulated lymphocyte populations in thalassemia may impair production of interferon-stimulated genes (ISGs), which are vital in suppressing viral replication and shaping virome dynamics [42]. Collectively, the immunological imbalances of lymphocytes observed in β-thalassemia patients not only weaken antiviral immunity but may also actively reshape the human virome, potentially contributing to persistent viral colonization, altered viral pathogenicity, and increased susceptibility to opportunistic infections (Figure 2) [8].

6. Iron Overload and Increased Virome Susceptibility in β-Thalassemia

Iron is a vital bio metal and an essential micronutrient involved in numerous fundamental biological processes, including cellular proliferation, redox reactions, DNA synthesis, cell cycle progression, and ferroptosis [43,44]. However, iron homeostasis is tightly regulated, as both deficiency and overload can result in significant cellular and organ damage. Iron overload is a well-recognized complication in β-thalassemia, affecting both transfusion-dependent (TDT) and non-transfusion-dependent (NTDT) individuals. In TDT patients, chronic blood transfusions lead to secondary iron accumulation in vital organs such as the liver and heart, increasing the risk of systemic iron toxicity [45]. In NTDT patients, ineffective erythropoiesis elevates serum erythropoietin levels while concurrently suppressing hepcidin expression, a key hormone that regulates systemic iron balance. This dysregulation enhances intestinal iron absorption and promotes iron deposition in tissues [46,47].

Beyond its physiological roles, iron is exploited by numerous viruses as a critical resource for replication, persistence, and pathogenesis [48]. Evidence suggests that excess iron promotes viral infection and progression, underscoring the potential impact of iron overload on the human virome. For example, in chronic hepatitis B virus (HBV) infection, elevated iron levels have been linked to enhanced disease progression and poor clinical outcomes [49]. Similarly, hepatitis C virus (HCV) patients often exhibit increased serum ferritin levels, which correlate with liver inflammation and hepatic iron deposi-

tion [50]. In the case of human immunodeficiency virus (HIV), iron availability facilitates viral replication within macrophages by promoting DNA synthesis and enhancing viral transcription [51,52]. Interestingly, while iron overload generally promotes viral infection, in some contexts—such as HCV and HIV—iron has been shown to inhibit certain viral processes, indicating a nuanced, virus-specific modulation of replication by iron levels [53]. These findings suggest that elevated iron levels in β-thalassemic patients not only increase host cell susceptibility to viral infections but also impair immune surveillance, potentially contributing to virome reshaping (Figure 3). Thus, iron may serve as a critical, yet often underrecognized, modulator of host virus interactions.

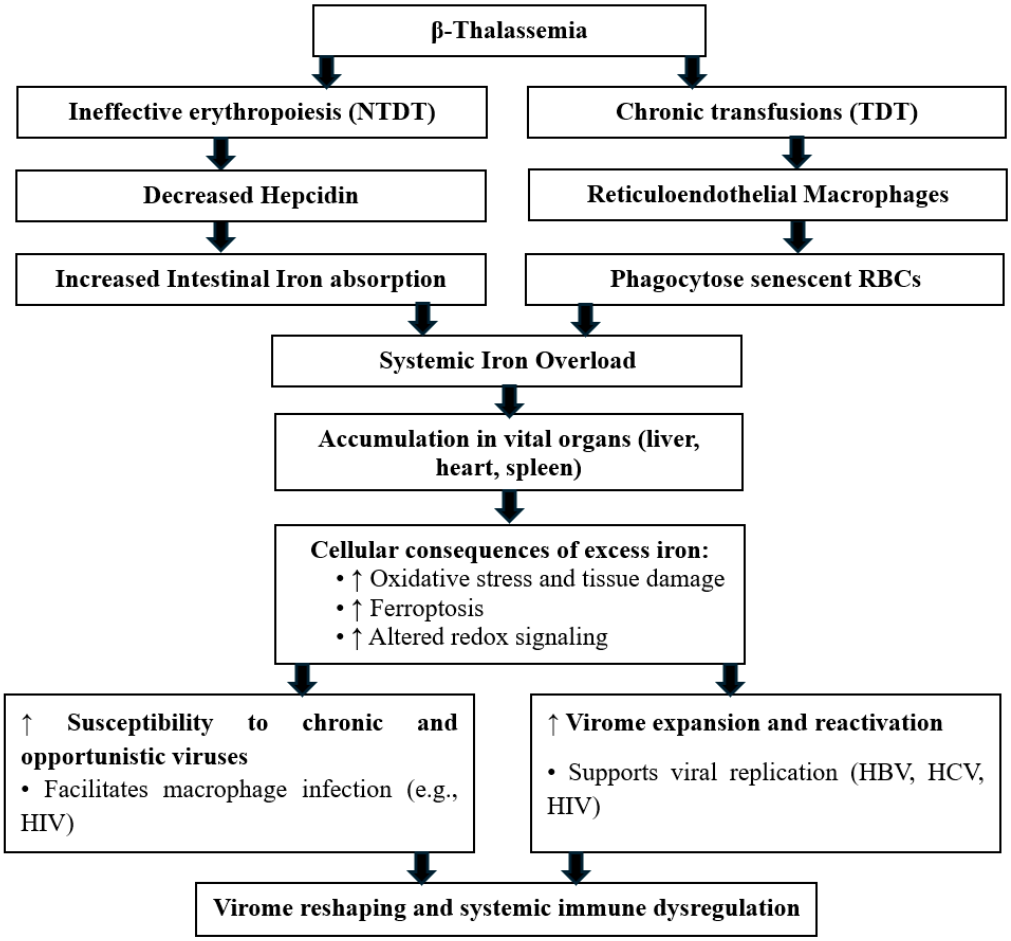


Figure 3. Iron Overload-Driven Modulation of Viral Susceptibility in β-Thalassemia. Iron overload in β-thalassemia arises from transfusion-dependent and non-transfusion-dependent mechanisms, leading to systemic iron accumulation and oxidative damage. Excess iron promotes viral replication and persistence by serving as a cofactor for DNA synthesis and viral transcription, particularly in pathogens like HBV, HCV, and HIV. Simultaneously, iron-induced immunosuppression weakens host defenses, enhancing virome diversity and reactivation. This positions iron as a critical modulator of host–virome interactions in β-thalassemia. "↑" indicates increasing.

7. Transfusion and Increased Virome Susceptibility in β-Thalassemia Patients

Transfusion-dependent β-thalassemia patients are uniquely vulnerable to virome expansion due to their lifelong reliance on donor blood. Although transfusion is a life-saving intervention particularly for individuals with β-thalassemia major (BTM), the most severe clinical form, it also introduces significant risks associated with transfusion-transmitted infections (TTIs). Inadequate donor screening, imperfect testing protocols, and suboptimal

blood processing in many resource-limited settings contribute to the inadvertent transmission of both well-characterized pathogens and lesser-known components of the human virome [54]. A landmark study analyzing the DNA virome of over 8000 individuals identified 94 distinct viral species in human blood, including human herpesviruses, anelloviruses, parvovirus B19, polyomaviruses, and high-risk oncogenic papillomaviruses such as HPV-16, along with HIV, HBV, and others [55]. This finding highlights the complex and diverse composition of the human blood virome, which can vary significantly by geography and ancestry, reflecting local epidemiological exposures and genetic susceptibilities [56].

In thalassemia, the cumulative effect of repeated transfusions not only increases the chance of exposure to known TTIs such as HBV, HCV, HIV, and human T-cell lymphotropic viruses (HTLV-I/II), but also facilitates the expansion of the patient's endogenous virome [54]. Each transfusion potentially introduces new viral species into the host, altering the balance between immune surveillance and viral persistence. Several studies have shown that thalassemia patients exhibit a disproportionately high prevalence of chronic viral infections. For instance, hepatitis E virus seroprevalence reached 27.15% among transfused thalassemia patients in Egypt [57], while in Iran, HEV prevalence ranged from 10–16.67%, markedly higher than in the general population [58]. Comparable data have been reported from Brazil (13%) and Saudi Arabia (10.7%) [59,60], suggesting a global trend.

Of particular concern is the persistent burden of HCV, which remains a major contributor to morbidity and mortality among thalassemia patients in regions such as India and Southeast Asia [61]. Notably, a earlier comprehensive mortality study identified viral hepatitis-induced liver disease (from HBV and HCV) as the second leading cause of death in β-thalassemia patients over the age of 15 [56]. This data underscores the long-term impact of transfusion-mediated viral exposure on survival outcomes. The clinical implications extend beyond liver disease, as viral persistence may interact with iron overload and immunosuppression to exacerbate inflammation and organ damage. Therefore, the transfusion practices in thalassemia, while essential, must be carefully balanced with stringent viral screening protocols, virome monitoring to minimize the introduction and propagation of pathogenic viral strains, early vaccination (anti-HBV, anti-HCV, and anti-HIV) [62], virome monitoring, and timely antiviral treatment (e.g., sofosbuvir, simeprevir, daclatasvir, Harvoni) [63]. Even seronegative blood may harbor occult viral infections, particularly in the context of high-risk populations or inadequate nucleic acid testing. Integrating these preventive and therapeutic strategies can markedly improve long-term survival in thalassemia patients.

8. Possible Role of Bacteriophages in Gut Dysbiosis and Immune Modulation in Transfusion-Dependent β-Thalassemia Patients

Transfusion-dependent β-thalassemia patients are particularly vulnerable to gut microbiota disruption due to cumulative effects from frequent blood transfusions, iron overload, oxidative stress, and broad-spectrum antibiotic use. These factors may introduce non-native bacteriophages (phages) into the gut ecosystem or destabilize existing microbial communities by increasing the number of free phage particles [55]. Phages, particularly those belonging to the *Caudovirales* order, play a central role in modulating the structure and function of the gut microbiome and have been implicated in the pathogenesis of intestinal inflammatory diseases such as colitis [64]. They facilitate horizontal gene transfer among bacteria, including the spread of virulence factors and antibiotic resistance genes, thereby reshaping microbial pathogenic potential [65]. Phage-mediated lysis of bacterial hosts can shift the abundance and diversity of commensal bacterial species, contributing to dysbiosis. Additionally, the release of nucleic acids during bacterial lysis acts as pathogen-

associated molecular patterns (PAMPs) that stimulate host immune responses and trigger inflammation through innate immune sensors [66].

A recent animal study showed that phages produced by pathogenic bacteria can be taken up by antigen-presenting cells and induce type I interferon (IFN) responses via TLR3- and TRIF-dependent pathways. This immune system inhibits TNF-α production and reduces bacterial phagocytosis, thereby impairing bacterial clearance and potentially increasing the risk of recurrent infections [66]. Furthermore, interactions between gut bacteria and eukaryotic viruses can also enhance viral infectivity and stability. For example, poliovirus has been shown to bind bacterial lipopolysaccharide (LPS), promoting virion stability and improving its fitness and persistence in the gastrointestinal tract [67]. These complex and reciprocal interactions highlight the underappreciated role of phages and the broader virome in immune dysregulation and gut health in β-thalassemia patients, suggesting a novel layer of complexity in transfusion-related complications.

9. Allogeneic Hematopoietic Stem Cell Transplantation and Reactivation Risk of Virus in β-Thalassemia Patients

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains the only potentially curative option for β-thalassemia major, offering a chance at transfusion independence and long-term survival [68]. While its clinical efficacy is well established, allo-HSCT carries substantial immunological risks, particularly in the context of viral reactivation following transplantation-induced immunosuppression. In patients with a history of resolved hepatitis B virus (HBV) infection, allo-HSCT has been associated with a high rate of reverse seroconversion, with one study reporting a 50% reactivation rate of HBV post-transplantation in β-thalassemia patients [69]. This underscores the vulnerability of previously latent or cleared viruses to re-emerge under conditions of profound immune dysregulation. Furthermore, acute graft-versus-host disease (aGvHD), a frequent complication of allo-HSCT has been shown to exacerbate this susceptibility [70]. In a recent study of 117 pediatric patients with β-thalassemia major who underwent fully HLA-matched related donor transplantation, approximately 43% developed aGvHD, with cytomegalovirus (CMV) reactivation observed in 39% of affected patients, particularly those with Grade II or III aGvHD [71]. CMV reactivation in this context not only reflects post-transplant immune suppression but also correlates with worse transplant outcomes and increased risk of secondary infections.

In addition to CMV, allo-HSCT recipients are at elevated risk for reactivation of a broad spectrum of latent viral pathogens comprising the human virome [72]. A comprehensive 11-year single-center analysis of pediatric patients undergoing allo-HSCT documented frequent reactivations of human herpesvirus 6 (HHV-6), Epstein–Barr virus (EBV), adenovirus (ADV), herpes simplex virus (HSV), and varicella-zoster virus (VZV), further emphasizing the wide range of virome components that become clinically relevant in the post-transplant period [71]. These findings are especially pertinent for β-thalassemia patients, who often undergo transplantation at a young age and may have prior viral exposures due to repeated transfusions. The interplay between transplantation, immunosuppressive therapy, graft-versus-host disease, and latent viral reservoirs collectively shapes the post-HSCT virome, increasing the complexity of clinical management in these patients. The nucleoside analogue lamivudine effectively prevents and treats HBV reactivation after HSCT. Additionally, vaccinating anti-HBs negative donors before allo-HSCT may help prevent reactivation in recipients with resolved HBV infection [68,69].

10. Risk of Virus Reactivation After Splenectomy in β-Thalassemia Patients

Splenectomy is a commonly employed therapeutic intervention in patients with β-thalassemia major (β-TM) to alleviate complications arising from hypersplenism, such as excessive red blood cell sequestration, cytopenias, and increased transfusion dependency [73,74]. The removal of the spleen typically results in reduced hemolysis, improved hemoglobin levels, and a notable decrease in transfusion frequency [75]. However, this clinical benefit comes at a considerable immunological cost. The spleen is a critical lymphoid organ involved in both innate and adaptive immune responses, particularly in filtering blood-borne pathogens, generating immunoglobulin responses, and supporting natural killer cell and T-cell development and function [76]. Its removal therefore compromises several immune surveillance pathways, increasing the host's susceptibility to infections, including reactivation of latent viruses.

In β-TM patients, this immunological impairment is further exacerbated by chronic iron overload, a consequence of regular transfusions and ineffective erythropoiesis, which promotes oxidative stress and suppresses phagocytic cell function. Studies evaluating immune profiles in splenectomized thalassemia patients have yielded varying results. While some have reported a decline in NK and $CD4^+$ T-cell numbers post-splenectomy [77,78], others have noted increased absolute counts of $CD4^+$ and $CD8^+$ T lymphocytes, albeit with diminished functional responsiveness [73]. These immune alterations may impair the body's ability to control latent viral infections, including herpesviruses, hepatitis B and C viruses, and other transfusion-associated viral pathogens, making splenectomized thalassemia patients more vulnerable to viral reactivation and opportunistic infections. Given these risks, careful monitoring, preoperative vaccination (*pneumococci*, *meningococci*, and *H. influenza* type b) and prophylactic measures (new protein conjugate vaccines, antibiotic prophylaxis, increased awareness, and patient education) are essential for patients with β-thalassemia who have undergone splenectomy [79].

In order to provide a comprehensive overview of the pathogenic pathways discussed above, we have summarized the key mechanisms in β-thalassemia that contribute to alterations in virome dynamics. These include both intrinsic immune defects such as neutrophil, lymphocyte dysfunction, and NK cell impairment as well as extrinsic factors like transfusion-related risks, iron overload, and splenectomy. Each of these factors uniquely influences viral replication, latency, persistence, or reactivation. Furthermore, emerging interactions between bacteriophage dysbiosis and eukaryotic virome behavior may exacerbate viral pathogenicity under conditions of immune compromise. Table 2 provides an integrated overview of these mechanisms, their associated immune effects, and the resulting shifts in virome composition and behavior in β-thalassemia patients.

Table 2. Pathogenic Mechanisms in β-Thalassemia and Their Impact on Virome Dynamics.

Patho Mechanism	Description	Affect	Changes in Virome	Ref.
Immune dysregulation: Neutrophils	reduction in neutrophil number and function	Viral persistence, reactivation, or opportunistic infection	HIV, hepatitis B and C viruses, rhinovirus, HSV-1, RSV, and influenza	[30]
Immune dysregulation: Lymphocytes (T Cell, B Cell, NK Cells)	Senescent $CD8^+CD28^-$ T, diminished telomerase activity, suppress dendritic cell activation	Influence viral replication, latency, and clearance	HIV, hepatitis B and C viruses, rhinovirus, HSV-1, RSV, and influenza	[30]

Table 2. *Cont.*

Patho Mechanism	Description	Affect	Changes in Virome	Ref.
Iron overload	Suppressing hepcidin expression, a key hormone that regulates systemic iron balance	Excess iron promotes viral infection and progression, Decreased NK activity	HIV, hepatitis B and C viruses	[49]
Transfusion	Suboptimal screening of blood donors, inadequate testing, and improper blood processing	Transfusion-transmitted infections(TTIs)	hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), West Nile virus (WNV), and human T-cell lymphotropic viruses I and II (HTLV-I/II).	[54]
Bacteriophage dysbiosis	Type 1 IFN inhibits TNF production and limits bacterial phagocytosis	Bacterial lipopolysaccharide enhances virion stability	Poliovirus	[67]
Clinical implications: allo-HSTC	various transplantation-related complications	Reactivation	human herpesvirus 6 (HHV-6), Epstein–Barr virus (EBV), cytomegalovirus (CMV), adenovirus (ADV), herpes simplex virus (HSV), and varicella-zoster virus (VZV)	[11]
Clinical implications: Splenectomy	Impaired hepcidin–ferroportin response	NK cell number and activity decrease	HIV, hepatitis B and C viruses	[73]

11. Conclusions: Future Perspectives

The emerging understanding of the human virome has shed light on its potentially critical role in shaping immune responses and influencing disease progression, especially in immunocompromised conditions such as β-thalassemia. In β-thalassemia patients, a unique convergence of clinical interventions including frequent blood transfusions, iron overload, splenectomy, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) creates an immunological environment that is highly susceptible to viral acquisition, reactivation, and persistence. Transfusions, while lifesaving, may serve as conduits for both pathogenic and commensal viruses, subtly expanding the circulating virome and altering the host's immune landscape. Splenectomy, commonly performed to reduce transfusion burden, compromises innate and adaptive immune functions, increasing vulnerability to latent viral reactivation and transfusion-transmitted infections. Allo-HSCT, though potentially curative, brings with it significant risks of reactivation of latent herpesviruses (e.g., CMV, EBV, HHV-6) and other opportunistic viruses, particularly in the presence of graft-versus-host disease.

Furthermore, emerging evidence suggests that bacteriophages, a major component of the gut virome, can disrupt microbiota homeostasis, promote intestinal inflammation, and modulate systemic immune responses in transfusion-dependent individuals. The interplay between phages, bacterial communities, and the host immune system may contribute to chronic inflammation, impaired viral clearance, and enhanced susceptibility to new infections. Together, these findings underscore the need to view the virome not just as a bystander but as an active participant in the pathophysiology of β-thalassemia.

A deeper understanding of virome dynamics in β-thalassemia could open avenues for better infection surveillance, virome-informed risk stratification, and targeted antiviral or microbiome-modulating therapies. As advanced sequencing technologies become more accessible, integrating virome profiling into routine clinical care may ultimately improve outcomes for thalassemia patients living under the constant threat of viral complications.

The integration of advanced screening tools, including nucleic acid testing and virome-based diagnostics, is essential to strengthen blood safety measures. Moreover, metagenomic and viromic sequencing technologies offer unprecedented opportunities to detect novel, latent, or low-abundance viruses that may escape conventional detection. These tools can enhance our understanding of virome diversity, enable the development of personalized antiviral strategies, earlier identification of high-risk viral reactivations, and improved post-transplant surveillance in thalassemic patients. Future studies are needed to clarify the comprehensive characterization of the DNA and RNA viromes at distinct body sites, particularly in immunocompromised and transfusion-dependent individuals. Such efforts will pave the way for integrating virome profiling into routine clinical care, ultimately advancing precision medicine and improving outcomes in vulnerable populations such as β-thalassemic patients.

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Abbreviations

The following abbreviations are used in this manuscript:

β-TM	Beta-thalassemia major
TI	Beta-thalassemia intermedia
TDT	Transfusion-dependent thalassemia
NTDT	Non-transfusion-dependent thalassemia
TTIs	Transfusion-transmitted infections
allo-HSCT	Allogeneic hematopoietic stem cell transplantation
CMV	Cytomegalovirus
HTLV-I/II	Human T-cell lymphotropic virus types I and II
MDSCs	Myeloid-derived suppressor cells
PTX3	Pentraxin 3
CXCR2/CXCL2	CXC chemokine receptor 2/chemokine ligand 2
LPS	Lipopolysaccharide
aGvHD	Acute graft-versus-host disease
VZV	Varicella-zoster virus

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