Thrombotic and cardiovascular events in HIV infection (Review)

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Received December 21, 2024; Accepted May 15, 2025

DOI: 10.3892/br.2025.2000

Abstract. Human Immunodeficiency Virus (HIV) infection has nowadays become a chronic disease, due to the introduction of antiretroviral therapy (ART), which has improved both life expectancy and quality of life of patients with HIV but has also led to the emergence of previously unrecognized complications. Thromboembolic events constitute a serious and frequent comorbidity in patients with HIV. The thrombogenic potential of HIV infection is multifactorial and is attributed to persistent chronic inflammation, endothelial dysfunction and ART itself, mainly through the resulting metabolic alterations. Co-infections and gut microbe translocation observed in patients with HIV, also maintain the inflammatory prothrombotic microenvironment. Individuals with HIV are at higher risk for venous thromboembolism and cardiovascular disease, compared with general population. Among patients with HIV, those receiving specific ART regimens have a significant higher risk for myocardial infraction. HIV infection is also involved in other coagulation disorders, such as heparin-induced thrombocytopenia and thrombotic thrombocytopenic purpura. Therapeutic choices do not differ from individuals without HIV but should be cautiously administered due to drug interactions. Further studies are required in order to fully understand the pathophysiological mechanisms involved and develop new treatment options for patients with HIV.

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Key words: HIV, antiretroviral therapy, venous thromboembolism, cardiovascular disease

Contents

1. Introduction

While Human Immunodeficiency Virus (HIV) infection continues to be the most common cause of Acquired Immune Deficiency Syndrome (AIDS), it is now considered a chronic condition rather than a fatal disease. This shift is attributed to the early initiation of prophylactic and therapeutic practices aimed at preventing opportunistic infections and other complications related to AIDS. However, despite these advancements, morbidity and mortality in patients with HIV persist, primarily due to non-AIDS-related conditions (1,2).

In this context, HIV infection has been linked to thromboembolic events. The systemic activation of the immune system and the inflammatory microenvironment, often intensified by co-existing infections in patients with HIV, create a prothrombotic state with diverse clinical manifestations (1,2).

2. HIV infection and thrombosis

HIV primarily targets $CD4^+$ T-lymphocytes, along with macrophages and dendritic cells, which in turn produce a variety of cytokines and chemokines with multiple roles, including IFN-γ, IL-6, IL-10, IL-12 and TNF-a (3). Infected and activated $CD4^+$ T-lymphocytes exhibit elevated levels of the NF-κB factor, promoting the genome transcription of the integrated virus. This leads to the production of new viral particles, resulting in a detrimental cycle of T-cell infection and activation. Simultaneously, the virus evades regulatory

immune mechanisms, inducing apoptosis in cells mobilized to control HIV infection. This series of events represents persistent immune system activation and an ongoing inflammatory process, inevitably intertwined with the coagulation pathway (3,4).

Immunothrombosis is the term used to describe this bidirectional interaction between coagulation and inflammation, mediated by cellular and non-cellular components of both systems (5). Endothelial cells are the first to be exposed to pathogens circulating in the blood via inflammatory mediators, such as the lipopolysaccharide of the microbial membrane. Loss of endothelial integrity results to platelet adhesion and activation, as well as expression of tissue factor (TF) on the endothelial surface, which acts as the initiator of the coagulation cascade (6). Activated platelets play multiple roles by releasing the content of their granules, which include pro-coagulant and pro-inflammatory substances [coagulation factors, ADP, TXA2, platelet factor 4 (PF4)] (6,7). Platelets also release microparticles (MPs) with procoagulant properties and express adhesion molecules, such as P-selectin, as well as negatively charged phospholipids on their surface, such as phosphatidylserine (PS), which constitutes the substrate to promote the coagulation process (6,7). P-selectin binds to P-selectin glycoprotein ligand-1 of endothelial and inflammatory cells, favoring the migration and activation of monocytes and neutrophils (7). P-selectin is also expressed by endothelial cells, being a site of attachment of neutrophils to the vascular wall (5).

HIV induces endothelial injury and activation of endothelial cells, with higher levels of endothelial MPs observed in patients with HIV compared with controls (8). Platelets have a variety of receptors, such as C-type lectin receptor 2, CC chemokine receptor 3 and integrin β3, which mediate interactions with HIV and may result in endocytosis of the virus and subsequent platelet activation (9). Patients with HIV display a high percentage of agranular platelets, increased plasma levels of platelet activation markers, and platelet MPs, all indicative of prior platelet activation (8,10). Activated platelets express higher levels of P-selectin, facilitating endothelial adhesion and secrete large amounts of CD40 ligand, thus recruiting monocytes and neutrophils (9). Importantly, HIV-infected individuals exhibit increased numbers of TF-expressing monocytes, along with higher TF plasma levels compared with controls. TF expression by monocytes correlates not only with elevated HIV plasma levels but also with various markers of immune system activation, such as CD38 and CD20 HLA-DR in $CD8^+$ T-lymphocytes and excessive sCD14 plasma levels (11). Furthermore, platelet-neutrophil interactions lead to NETs formation, a scaffold made of extracellular nucleic acids, histones, enzymes, white blood cells and coagulation factors, which further contributes to a prothrombotic state (9,12).

Co-infections, including mycobacterium tuberculosis, cytomegalovirus and pneumocystis pneumonia, contribute to immune system activation in patients with HIV (13). The destruction of the gastrointestinal (GI) mucosal barrier, leading to the microbial shift, is caused by the depletion of $CD4^+$ memory T-cells in the GI tract during the early stages of infection. This depletion persists despite therapeutic interventions, resulting in the loss of GI tract integrity, microbial translocation and activation of the innate immune system (3,14).

Emerging evidence has indicated that gut microbiota plays a significant role in thrombosis through its influence on inflammation, metabolism and coagulation pathways. Gut microbiota-derived metabolites, such as trimethylamine-N-oxide (TMAO), choline and betaine have been associated with cardiovascular disease (CVD) in a variety of clinical settings, by promoting endothelial dysfunction, impairment of liver cholesterol metabolism and platelet aggregation, mostly by increasing platelet sensitivity to various stimuli (15). A recent study of COVID19-infected patients has shown that 2-methylbutyrylcarnitine, a branched-chain acylcarnitine, augments platelet hyperreactivity by binding to platelet integrin α2β1 and potentiating phospholipase A2 activation, thus contributing to a hypercoagulable state (16). In the context of HIV infection, HIV-related gut dysbiosis along with microbial translocation may contribute to endothelial activation and thrombosis. However, robust evidence still lacks. A recent study of HIV-infected women has demonstrated that microbial metabolite imidazole-propionate has been correlated with several inflammatory markers and carotid artery plaque. Nonetheless, these findings warrant further research, since development of agents targeting these pathways, such as TMAO inhibitors, along with dietary interventions may help reduce thrombotic complications and CVD in patients with HIV (17).

Furthermore, HIV-associated malignancies, along with reported acquired deficiencies in protein C, S, and antithrombin, increased antiphospholipid antibodies, and elevated vWF levels, contribute to the prothrombotic state observed in patients with HIV (13).

Consequently, a variety of factors and their complex interactions end up in the state of chronic inflammation, chronic immune system activation, platelet and endothelial dysregulation, thus promoting thrombosis.

3. Antiretroviral therapy (ART) and thrombosis

Modern ART, which involves co-administering drugs targeting distinct pathways of HIV infection, has significantly enhanced the quality of life for patients with HIV. This is achieved by reducing plasma viral load, preventing HIV transmission, and curbing drug resistance, ultimately leading to a decrease in mortality rates. Despite these benefits, ART has been linked to thrombotic events and heightened cardiovascular risk.

Previous studies have demonstrated that markers of platelet activation, such as sCD62P, sCD40L, CD62P and RANTES, remain elevated, even during successful ART, and may persist for several months (18-20). Opposingly, a study of platelet function in patients with HIV on ART has reported normalization of markers of platelet activation by 12 months post-ART initiation (21). A previous meta-analysis has shown that platelet reactivity persists despite initiation of ART (18). In particular, levels of sCD62P and surface CD62P remained significantly elevated following effective ART, thus suggesting that long-term HIV infection is correlated with a prothrombotic state despite its control with ART (18). A study has previously shown that TF-expressing monocytes are increased in HIV-infected patients as compared with healthy individuals and that monocyte TF levels remain elevated, despite administration

of suppressive ART, thus indicating that the persistent coagulopathy observed in these patients may be attributable to monocytes and TF (22).

Intriguingly, it has been shown that raltegravir, an integrase inhibitor, is associated with reduced platelet reactivity and reduced platelet monocyte aggregates (19,23), whereas abacavir (ABC)-containing regimens is associated with increased platelet activation, thus indicating that the type of antiretroviral agent may have impact on thrombotic risk (19). Results from a large cohort of contemporary-treated patients with HIV have indicated that recent ABC use is associated with increased risk for CVD (24). However, a recent meta-analysis has not found a significant association between ABC use and CVD incidence rate (25). Although there is ongoing debate as to whether ABC is associated with increased thrombotic risk, recent data have suggested that ABC may promote thrombosis by increasing prothrombin conversion and by inducing the release of soluble low-density lipoprotein receptor-1, which in turn leads to platelet activation (26,27). Regarding integrase strand-transfer inhibitors (INSTIs), despite the previous reports of raltegravir-induced reduction of platelet reactivity, recent data have suggested that treatment with INSTIs is associated with an elevated risk for CVD in the first 24 months after treatment initiation, which thereafter decreases to levels similar to those never exposed to INSTIs (28). Moreover, INSTIs regimens have been linked to greater weight gain but improved lipid metabolism profiles among individuals with HIV (29).

Among antiretroviral agents, protease inhibitors (PIs) display significant thrombotic risk. Increased levels of markers of platelet activation have remained largely unchanged in patients with HIV following PI treatment initiation (18). PIs within ART may impact coagulation proteins through hepatic metabolism and are associated with abnormal coagulation parameters, especially when combined with nucleoside reverse transcriptase inhibitors (NRTI) regimens, resulting in elevated fibrinogen levels (10,13). Patients on ART, particularly those on PI regimens, may experience metabolic disorders such as lipodystrophy and various abnormalities in lipid and glucose metabolism (30). Endothelial dysfunction has also been observed in individuals on ART, specifically those on PI or non-NRTI (NNRTI), attributed to reduced nitric oxide (NO) levels, increased production of reactive oxygen species, and alterations in lipid metabolism (8). A study involving patients with HIV treated with PIs/NNRTIs revealed higher serum levels of soluble endothelial dysfunction markers (P-selectin, tissue Plasminogen Activator) compared with those not receiving therapy (31). PIs ritonavir and indinavir have been directly associated with endothelial dysfunction, linked to mitochondrial DNA damage and cell death (8).

Despite these findings, the precise pathogenetic pathways underlying the metabolism, endothelium, and coagulation alterations induced by ART have not been fully elucidated. Furthermore, thrombogenic potential of novel agents incorporated in the treatment of HIV, such as cabotegravir and lenacapavir needs to be elucidated. LATTE-2 Study, a study of efficacy and safety of long-acting cabotegravir and rilpivirine has reported occurrence of thrombotic events in four patients, which however were not drug-related (32).

Nonetheless, further research is warranted, and more randomized clinical trials should be conducted, thus safe conclusions, regarding the thrombogenic potential of various antiretroviral agents can be drawn. A summary of different classes of antiretroviral drugs and their thrombotic potential is presented in Table I.

4. Thrombotic events in patients with HIV

The multifactorial pathophysiological mechanism of thrombosis in HIV, as depicted in Fig. 1, leads to a wide spectrum of thrombotic events, including venous and arterial thrombosis, thrombosis in unusual sites and thrombotic microangiopathy.

Venous thromboembolism (VTE). The reported incidence of VTE in patients with HIV ranges from 0.19-7.63% per year, compared with 0.1-0.18% per year in general population (13,33). In a study by Sullivan *et al* (34), including 42,935 HIV-infected individuals, the incidence of thrombosis was 2.6/1,000 person-years (PY), calculated over a period of average 2.4 years. In a Danish study of 43,330 patients with HIV, the 5-year risk of VTE was estimated at 8.0% and 1.5% for intravenous drug users (IDU) and non-IDU individuals respectively, compared with 0.3% in the control group (35). The observed fluctuation in the incidence of VTE is attributed to the different number of patients included and the different duration of the studies. Additionally, some studies were performed before the universal application of ART.

Patients with HIV and uninfected controls with a history of VTE (first episode) were included in the study by Rokx *et al* (36), in order to determine the risk of recurrent VTE (36). The first episode of VTE was unprovoked in the majority of patients with HIV (71% vs. 34% in controls) (36,37). Recurrence rates were 5.2 and 3.1 per 100 PY of follow-up for HIV and uninfected individuals respectively (36). The higher incidence of recurrent VTE also applied for all HIV subgroups (men, women, patients with provoked or unprovoked first VTE episode) (36,37). During the five-year follow-up of study subjects, after discontinuation of anticoagulant therapy, the risk of recurrent VTE appeared to increase gradually, with the highest incidence at 5 years (23.4% vs. 15.3% in controls) (36,37). VTE recurrence was markedly reduced in patients with HIV who were immunodeficient during the first VTE episode and showed an improved response to ART, as reflected by $CD4^+$ T cell counts (36,37).

Clinical manifestations and the distribution of VTE in individuals with HIV do not differ significantly from non-HIV individuals. This includes occurrences of low extremity deep vein thrombosis, pulmonary embolism, and less common sites of thrombosis, such as splanchnic vein and cerebral vein thrombosis (CVT) (13,34). According to Sullivan *et al* (34), identified risk factors for VTE in patients with HIV include opportunistic infections, the administration of megestrol acetate or indinavir, hospitalization and an age of ≥45 years.

Regarding thrombosis at unusual sites, isolated cases have been documented in the literature. In a study of 26 HIV-infected individuals with CVT in India, elevated homocysteine levels and decreased vitamin B12 levels were noted. The clinical course of these patients was milder compared with HIV-negative patients with CVT, and they exhibited an improved response

Table I. A summary of different classes of antiretroviral drugs and their thrombotic potential.

Drug class	Mechanism	Thrombotic outcomes	Studies/comments
NRTIs, specifically Abacavir	Platelet activation, prothrombin conversion, release of soluble LOX-1	Risk of MI and probably other cardiovascular events	Conflicting evidence in studies (24-27). NRTIs combined with PIs may influence coagulation parameters (10,13).
INSTIs	↑ cardiovascular risk during first 24 months, then ↓	Cardiovascular events soon after initiation of treatment	Risk reduces over time (28). Weight gain, improved lipid profile (19,23,29)
Raltegravir (INSTI)	↓ Platelet reactivity, ↓ platelet-monocyte aggregates	Probably reducing thrombotic risk	
PIs	Platelet activation, ↑ fibrinogen, lipodystrophy-lipid/glucose disorders, endothelial dysfunction	Risk of cardiovascular events-especially MI, VTE	Ritonavir and indinavir particularly implicated. PIs combined with NRTIs may influence coagulation parameters. PIs combined with NNRTIs: higher levels of endothelial dysfunction markers (8,10,13,18,30,31,39)
Non-NRTIs	Endothelial dysfunction, ↓ NO, ROS production, lipid disorders	Risk of cardiovascular events	NNRTIs combined with PIs: higher levels of endothelial dysfunction markers (8,31)
Novel agents	No mechanism identified	No confirmed thrombotic risk	Thrombotic events not drug-related-LATTE 2 study (32).
Cabotegravir (long-acting INSTI)	Unknown	Unknown	Further studies required
Lenacapavir (capsid inhibitor)			Further studies required

NRTIs, nucleoside reverse transcriptase inhibitors; INSTIs, integrase strand-transfer inhibitors; PIs, protease inhibitors; LOX-1, low-density lipoprotein receptor-1; MI, myocardial infraction; VTE, venous thromboembolism; NO, nitric oxide; ROS, reactive oxygen species.

to therapeutic interventions (38). Ramanampamonjy *et al* (39) reported four cases of HIV-infected patients with portal vein thrombosis, showcasing severe immunodeficiency, PI regimens, and co-infections (hepatitis C, tuberculosis) in some or all of these cases.

However, although thrombotic risk is amplified in HIV-infected individuals, the exact incidence and risk factors still remain largely unclear.

Arterial thrombosis and CVD. CVD is one of the leading causes of morbidity and mortality, not only worldwide, but also in patients with HIV. In fact, in comparison individuals without HIV, patients with HIV have twice the risk for CVD, while the global percentage of HIV-related CVD has tripled in the last 20 years and accounts for 2.57 million disability-adjusted life years per year (40). CVD and sudden death were also the most common causes of death, at a rate of 19.31%, among patients with HIV in the SMART and ESPRIT studies (41).

Interestingly, the cardiovascular profile of patients with HIV is notably and more frequently impacted by traditional risk factors compared with individuals without HIV. These include factors such as obesity, hypertension, smoking, and disorders in lipid/glucose metabolism (30).

Thus, chronic inflammation, endothelial dysfunction and early atherosclerosis are implicated in HIV-related CVD (42). Introduction of ART has significantly increased survival rates of HIV-infected individuals, making aging an additional cardiovascular risk factor in these patients, while at the same time, ART itself has been associated with metabolic disorders and an increased CVD risk (8,42). In a meta-analysis of 2012, patients with HIV not receiving ART had a 1.61-fold higher risk and patients with HIV receiving ART a 2-fold higher risk of CVD than individuals without HIV. Among HIV-infected patients, those on ART had a 1.52-fold higher CVD risk than treatment-naïve individuals (43).

However, although HIV and ART exacerbate traditional cardiovascular risk factors, recent data have not indicated a statistically significant association of increased incidence of CVD with HIV-specific factors, such as use of specific antiretroviral agents (ABC, efavirenz) (25).

Myocardial infraction (MI). Focusing on MI, in a meta-analysis by Gutierrez *et al* (44), patients with HIV were at 1.6-fold higher risk of acute coronary syndrome than HIV-negative controls (44). In another, 2019 meta-analysis, the relative risk of MI in patients with HIV receiving ART and in untreated

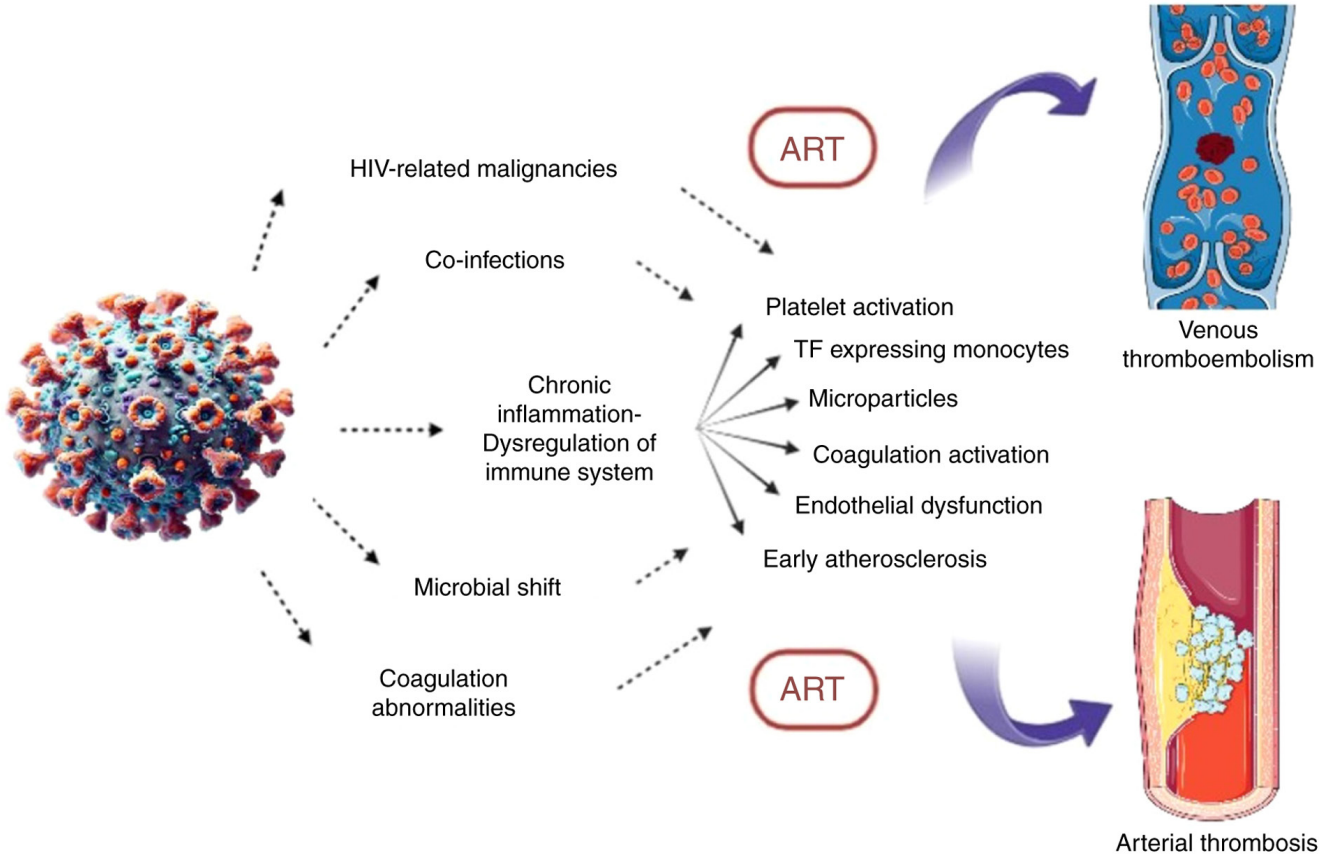

Figure 1. Pathophysiological mechanisms involved in venous and arterial thrombosis in HIV infection (26). The figure illustrates the complex interplay between HIV infection, chronic inflammation and thrombosis. Immune system dysregulation, in combination with HIV-related malignancies, co-infections, microbial shift, and coagulation abnormalities, trigger a cascade of prothrombotic mechanisms: platelet activation, tissue factor-expressing monocytes, microparticle release, coagulation activation, endothelial dysfunction, and early atherosclerosis. ART can also contribute and enhance these processes, ultimately leading to increased risk of venous thromboembolism and arterial thrombosis. ART, antiretroviral therapy.

patients with HIV was 1.80 and 1.25 respectively, both compared with uninfected individuals (45). In the same study, low $CD4^+$ T-lymphocyte counts (<200 cells/mm^3), increased plasma viral copies (>100,000 copies/ml) and ART, more specifically exposure to certain ART regimens and duration of administration, were associated with an increased MI risk (44,45).

Among the different classes of antiretroviral drugs, NRTIs and PIs were related to a greater risk of MI, with ABC (NRTI) and indinavir (PI) having the highest relative risks (1.71 and 1.46 respectively) (45). Administration of NNRTIs, either alone or in combination with other antiretroviral drugs, was not associated with increased incidence of MI (45).

Stroke. In the pre-ART era, HIV-infected individuals had a 2,3-fold higher risk of stroke than uninfected individuals, with cerebral infraction being the most common event in patients with HIV, as shown in a retrospective study from 1990 to 1994 (46). In a 2017 meta-analysis, the estimated risk of stroke in HIV compared with non-HIV individuals was 1.82 and 1.27, specifically for ischemic stroke (44). Regarding ART, no antiretroviral drug class was associated with an increased risk of ischemic stroke (44).

In addition to traditional and HIV-related cardiovascular risk factors, as aforementioned, opportunistic infections affecting the central nervous system, such as tuberculosis meningitis, neurosyphilis, and varicella-zoster virus, are also involved in the pathophysiology of ischemic attacks in HIV-infected patients (47). This may be one of the reasons why viral suppression in patients with with HIV, as reflected in high $CD4^+$ T-lymphocyte counts and low plasma HIV-RNA levels, may reduce ischemic stroke risk (48).

HIV-related thrombotic thrombocytopenic purpura (TTP). HIV can be one of the numerous causative factors of secondary TTP, with a 15-40-fold higher incidence in this patient group (49). It occurs more frequently in patients with advanced HIV infection, reduced $CD4^+$ T-cell counts and various comorbidities, such as Kaposi's sarcoma and cryptococcal meningitis (50).

Inflammatory cytokines participating in HIV infection may induce the endothelial release of ultra-large von Willebrand factor (ULVWF) multimers and downregulate the synthesis of ADAMTS-13 protein, which is the cleaving protease of ULVWF. Autoantibodies against ADAMTS-13 have been detected in some, but not all, HIV-infected patients (51).

Heparin-induced thrombocytopenia (HIT) and HIV. A higher risk of HIT was reported in patients with HIV compared with non-HIV-infected patients, when treated with heparin. Considering that dysregulated immune responses and various autoimmune manifestations have been documented in

individuals with HIV, chronic activation of the immune system in these patients may be implicated in the formation of antibodies against platelet factor 4 (PF4)-heparin complex (52).

5. Therapeutic and prophylactic measures in HIV-related thrombosis

Currently, there are no specific guidelines regarding antithrombotic and thrombolytic therapy in patients with HIV. However, in the event of an established venous or arterial thrombotic event, therapeutic management should not deviate from that for HIV-negative patients (13,53). It is crucial to pay special attention to potential interactions between ART and antithrombotic agents. Numerous antiretroviral agents impact CYP450 metabolism, leading to fluctuations in drug concentrations, which may affect medications like warfarin and direct oral anticoagulants (53). Moreover, low molecular weight heparin may be a preferable therapeutic option, given the higher risk of developing HIT with unfractionated heparin in patients with HIV (52). The duration of anticoagulant therapy in a confirmed VTE case should be tailored to each patient, generally continuing in the case of unprovoked VTE episodes, similar to uninfected individuals (37).

Modifying traditional cardiovascular risk factors remains an essential preventive measure in individuals with HIV. However, there is insufficient data concerning pharmaceutical prophylaxis with anticoagulant and antiplatelet agents in these patients. Various antithrombotic agents, including aspirin, clopidogrel, vorapaxar and edoxaban, have been utilized in different studies to assess their impact on inflammation, platelet activation and coagulation. Among these, clopidogrel has shown the most favorable results in reducing inflammatory biomarkers (42).

Due to the association of ART with lipid disorders, the initiation of antilipidemic therapy, when and where appropriate, should be integrated into the management algorithm for these patients. This integration should always consider potential interactions with ART agents (30).

There is a clear need for studies exploring novel treatment options for HIV-infected patients, aiming to minimize drug interactions and improve control of chronic inflammation and thrombosis. With the effective HIV suppression achieved by modern ART, future research could focus on incorporating immunomodulatory agents that inhibit major inflammatory markers, such as IL-1β, IL-6 and TNF-α (42). IL-1β is a key pro-inflammatory cytokine that promotes endothelial dysfunction, TF expression and platelet activation, ultimately leading to a prothrombotic state. Administration of canakinumab, a monoclonal antibody against IL-1β, has been shown to significantly reduce cardiovascular events in patients with prior MI, independent of lipid levels (54). Similarly, previous studies have shown reduced cardiovascular events with the use of anti-TNF agents and IL-6 inhibitors such as sarilumab in patients with autoimmune diseases, thus implicating a potential role of these agents in reducing thrombotic risk (55,56). Additionally, investigating specific biomarkers in HIV-infected patients and their role in thrombotic events and antithrombotic therapy, such as $CD4^+$ T cell levels, could represent a promising direction for future research (37) Finally, given the heterogeneity of the underlying mechanisms driving thrombosis in patients with HIV, individualized strategies should be adapted, which should also include development of assessment tools for thrombotic risk profiling, incorporating markers of platelet activation, such as sCD40L and sCD62P as well as the type of agent used.

6. Conclusion

In summary, HIV infection represents a prothrombotic situation, with patients being at increased risk for venous thromboembolic events, MIs and ischemic strokes. Various pathophysiological mechanisms are involved in the establishment of a thrombotic event in HIV infection, with the major ones being chronic inflammation, endothelial dysfunction and platelet and coagulation activation, enhanced by co-existing infections, acquired coagulation abnormalities and HIV-related malignancies. Specific ART regimens have also emerged as significant contributors to the HIV procoagulant state and have been incriminated for increased MI risk. An individualized therapeutic approach, taking into consideration the risk-benefit assessment and the potential drug interactions with antithrombotic agents, should be made for each patient, while further studies will explore the role of novel anti-inflammatory agents in the HIV thrombotic process.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

GD developed, planned and supervised the project, and wrote the manuscript. MV performed data entry and evaluation and wrote the manuscript. MP and AG developed and supervised the current study and wrote the manuscript. TP, VZ and DS, collected relevant literature. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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