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Chapter

Challenges in Platelet Functions in HIV/AIDS Management

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Abstract

The interest in platelet functions in HIV/AIDS is due to the high incidence of microvascular thrombosis in these individuals. A lot of laboratory data have been generated regarding platelet functions in this population. The tests demonstrate platelet hyperactivity but decreased aggregation, though results are inconsistent depending on the study design. Antiretroviral treatments currently in use display complex interactions. Many studies on platelet functions in these patients have been for research purposes, but none have found utility in guiding drug treatment of thrombosis.

Keywords: HIV, AIDS, platelet functions, light transmission aggregometry, flow cytometry, microparticles, combined antiretroviral, antiplatelets

1. Introduction

There is increasing focus on platelet functions in people living with HIV/AIDS. This is because of the high incidence of cardiovascular events in these individuals that is 10 times higher than general population [1] independent of traditional risk factors such as age, hyperlipidemia, and ethnic/racial differences. Acquired platelet dysfunctions are often observed in association with HIV/AIDS. Of the available tests for platelet functions [2, 3], none fully captures the complexity involved in this population group.

The results of the functional assays are modified by the viral count, CD4/CD8 ratio, and immunological response and whether or not on antiretroviral treatment. The effects of combined antiretroviral therapy (cART) on platelet functions are complex. Despite achieving viral suppression, these drugs have been demonstrated to have independent effects on platelet functions.

2. Platelet count and indices in HIV/AIDS

Complete blood count and microscopic examination of formed elements are often the first investigations in suspected hemostatic disorders in clinical situations. Platelet count and morphological changes have impact on bleeding or thrombosis.
2.1 HIV-associated thrombocytopenia

Globally, the prevalence of HIV-associated thrombocytopenia is 4–40% [4] though there are geographical, racial as well as ethnic differences from the same locality [5] and stage of disease. Indeed, thrombocytopenia has been considered as a marker of disease progression and improvement [6]. Whereas platelet counts improve with initiation of combined antiretroviral therapy (cART) viral suppression [7], beneficial effect does not apply to zidovudin (AZT) [8].

Despite thrombocytopenia, very low rates of clinical hemorrhage have been reported, estimated at only 3.2% among HIV thrombocytopenic patients [9] even with platelet count as low as $50 \times 10^9/L$ [10] casting doubt on the clinical relevance of the laboratory results. As a result of lack of clear correlation between HIV-associated thrombocytopenia and clinical significance, some authors have questioned benefit of treatments purely directed toward improvement of platelet count [11].

2.2 HIV-associated thrombocytosis

The prevalence of HIV-associated thrombocytosis, defined as platelet count of more than $400 \times 10^9/L$ [12], is low but depends on the population studied and concurrent medications. Reported prevalence of thrombocytosis in pediatric group who were also HIV-positive cART naive was found at 6% [13], though could be higher at 14% (more than thrombocytopenia at 7% in same cohort) for children on co-trimoxazole prophylaxis [14]. Whether these findings were independent or dependent on co-administered drugs remains undetermined.

Thrombocytosis is an emerging toxic complication accounting for 9% on stable cART depending on the regimen [7] up from 5.8% in treatment-naïve individuals [7]. It remains undetermined the relationship between HIV-associated thrombocytosis and accelerated thrombosis.

2.3 Platelet ultrastructure in HIV/AIDS

Despite the thrombocytopenia being associated with HIV, peripheral blood film smears of platelets are either unremarkable or hypogranular, which are of different sizes appearing as fragments [15].

Ultrastructure of platelets from HIV individuals, apart from showing normal features of hyperactivated aggregates having membrane pseudopodia/filopodia formation, in addition have shriveled aggregates with irregular and torn membrane surfaces, membrane blebbing and shedding of vesicles [16, 17]. The most distinctive features are alteration of granular structure though data are limited.

3. Tests based on platelet aggregation

3.1 Light transmission aggregometry (LTA)

Most studies on platelet aggregation in HIV have used single or fewer than the recommended panel of agonists with conflicting results [18]. Application of escalating agonist concentrations has uncovered dose-response patterns [19]. In this study, while epinephrine demonstrated greater potency indicating hyperresponsiveness, responses with collagen, TRAP, and ADP showed lesser maximum aggregation indicating
lesser efficacy and hyporesponsiveness. The agonist dose-response curve is, however, modified by cART viral suppression, especially abacavir-containing regimens [20] depending on agonist [21]. It must be remembered that although cART is a commonly mentioned modifier, the effects of fever associated with HIV are neither reported nor analyzed in these studies. Hyperthermic conditions such as fever are associated with reduced platelet aggregation [22].

3.2 Whole blood platelet aggregometry—multiple electrode aggregometry (MEA) and impedance aggregometry

A study comparing whole blood platelet aggregation using MEA found hyporeactivity in both HIV-treated and untreated individuals [23], similar to findings by impedance aggregometry [24]. It is worth noting that co-infection with HBV (6 vs. 4%) and HCV (0 vs. 2%) and low CRP levels [23] could have obscured the overall response. Co-infection with other viruses modulates platelet responses in HIV [25].

3.3 Thromboelastography (TEG)/ Thromboelastometry (ROTEM)

Few studies have been performed using thromboelastography (TEG) in HIV individuals. Of the few studies done, MA amplitude was low despite higher normal fibrinogen levels in both cART-treated [21] and untreated HIV subjects [23]. These study results of hypocoagulability are not in keeping with other tests, probably reflecting lack of sensitivity of TEG as a platelet function assay.

4. Platelet activation

Activated platelets are characterized by surface expression of activation-specific molecules such as P-selectin or CD62P, active GPIIbIIIa (PAC-1), phosphatidylserine (PS) externalization; platelet-leukocyte aggregates (PLA); platelet microparticle formation (PMP), in addition to granule secretion such as platelet factor 4 (PF4), β-thromboglobulin, and intracellular calcium flux [26].

4.1 Flow cytometry for membrane surface glycoprotein expression

A number of studies have documented platelet hyperactivity in HIV characterized by increased plasma membrane surface expression of CD62P, PAC-1, PS, CD63, [27], but paradoxically decreased GPIbα [28]. The levels positively correlate with viral loads but not CD4 count [29].

Although activation markers are higher in HIV sero-positive individuals who are cART naïve compared to healthy controls [30], with cART treatment levels decrease but do not normalize to pre-treatment levels [20, 31]. The persistent levels are related to inflammatory markers in virally suppressed individuals [32].

4.2 Intracellular signal transduction test—VASP

There is evidence of altered signal transduction affecting protein synthesis, degranulation, and activation functioning in HIV platelets. Experimental data show that HIV platelets had upregulation of ABCC4 (ATP-binding cassette subfamily 4), increase in cAMP, decrease in vasodilator-stimulated phosphoprotein (VASP),
which correlated with increased membrane expression of CD62P and integrin αIIbβ3 (GPIIbIIIa) [33]. It must be noted that VASP is only sensitive to PY12 inhibitors, and not much data are available from HIV patients.

5. Platelet secretion

5.1 Alpha granules

People living with HIV have increased secretion of alpha granule contents such as RANTES, sP-selectin, and sCD40L [34], despite viral suppression [33]. The persistence of these chemokines, especially anomalous secretion of RANTES, despite cART treatment [28] remains unexplained to date.

5.2 Dense granules

HIV platelets have low basal dense granule content and diminished secretion response as evidenced by low mepacrine uptake and release [33]. Although platelet mepacrine uptake and release have been considered among dense granule assays, it is not as specific as serotonin and lummiaggregometry for ATP [35, 36]. Despite this knowledge, the measurements of platelet serotonin and ATP remain largely undescribed in people living with HIV.

5.3 Concept of “platelet exhaustion” in HIV

Although HIV-associated platelets display increased baseline expression of surface activation markers compared to healthy controls [32], there is evidence of refractoriness to further agonist stimulation. This behavior has been referred to as “platelet exhaustion” in many publications [25, 28, 32, 37, 38].

Platelet “exhaustion” as a concept was postulated in references to previous observations, before HIV era, where activated platelets continued to circulate [39, 40] and were shown to be activated [41] but with decreased aggregation [42, 43]. They were considered refractory to further agonist stimulation [44] owing to acquired storage pool granule depletion [45, 46].

In HIV, stimulation with increased agonist concentration leads to lesser response at each corresponding dose [21]. Specifically, decreased thrombin dose-response curve for granule content and secretions for P-selectin, PFA/CXCL4,TXA and RANTES in HIV platelets less than healthy controls [32]. The decreased P-selectin and PAC-1 secretory responses correspond to impaired c-AMP, ABCC4 and VASP signal transduction mechanisms [33]. Furthermore, HIV platelets display decreased mepacrine uptake and release [33], and wheat germ agglutinin staining (WGA) [32] indicating reduction of dense and alpha granule contents respectively.

Despite many studies mentioning “platelet exhaustion” in HIV, however the results in support are neither consistent for all agonists nor confirmed by other tests. In patients who are cART naïve, stimulation with AA, ADP or collagen, the dose-response curves for CD62P are higher than the uninfected controls [30]. None of the LTA aggregation tests have been accompanied by corresponding Lumiaggregometry test which could have better characterized platelet ATP dense granule secretion [47, 48]. Platelet lumiaggregometry testing remains largely un-described in HIV.
Furthermore, the studies are on people who are already infected by HIV, but platelet responses prior to HIV infection remains unknown.

From the foregoing, evidence in support for “platelet exhaustion” in HIV is suggestive but inconclusive. Although decreased dose-response to thrombin has been described, however response to epinephrine was enhanced in some studies. The maintained response to epinephrine casts doubt on granule exhaustion, since true storage pool disorder do not respond to epinephrine [49] or variable [50]. Indeed HIV platelets maintain both alpha and dense granule secretions to collagen and ADP agonists stimulation [51]. Perhaps a better term to use could be “anergy,” refractory or “tired” platelets.

6. Platelet adhesion

HIV platelets have enhanced adherence to fibrinogen-coated surfaces [32, 33]. However, testing by this method is technically difficult and not available in clinical situations.

Although platelet PFA-100/200 testing is always recorded as aggregation in most studies, in actual fact it is marker of adhesion [2, 52]. The few tests of PFA-100 in HIV compared those on cART treatment with untreated [31], or in addition to [53] all of which showed shorter closure time in treatment-naïve individuals. The short closure times were neither normalized with aspirin nor with cART. The results are strongly indicative of influence of vWF as a third dimension in platelet function testing [54, 55].

7. vWF-ADAMTS-13 axis in HIV/AIDS

People living with HIV (PLWHIV) despite having very low platelet counts do not have issues of bleeding [56–58]. Instead, HIV-associated thrombotic complications [59] are an emerging issue of concern [60]. Although congenital thrombotic thrombocytopenic purpura (TTP) is very rare, acquired TTP is on the increase and associated with HIV estimated to be 15–40 times than the HIV negative in the general population [61]. It has been reported that HIV is responsible for 80% of TTP cases [62].

TTP is characterized by reduced or absent ADAMTS-13 and elevated vWF antigen as well as activity [63] especially the Unusually Ultralarge vWF multimers [64]. Elevated vWF Ag and high-molecular-weight vWF multimers [65] with reduced ADAMTS-13 have been detected in acute and chronic HIV [66, 67] and those with confirmed thrombosis [68]. Unusually, ultra large vWF multimers that have increased adhesion to platelet GPIbα-V-IX receptors [69] compensates for hemostasis in the presence of the low platelet count in HIV.

8. Platelet microparticles

It has been demonstrated that blood from HIV individuals have abundant circulating platelet microparticles [70], and this is despite viral suppression [71, 72]. The levels were associated with increased cellular ROS, caspases, eNOS [72], and mitochondrial membrane depolarization [73] indicative of apoptosis [74]. Further,
co-existence of platelet microparticles with increased LPS and platelet P-selectin and TF [29] are strong indicators that they are products of platelet activation.

9. Mechanisms of platelet activation in HIV

9.1 Direct effect of HIV

Recently, in mice, HIV particles were shown to be endocytosed by platelets by binding to TLR-7&9 leading to increased secretion of alpha (PFA-4) and dense granules (serotonin), and membrane expression of P-selectin [75]. Additionally, HIV interacts directly with platelets CLEC-2 and DC-SIGN receptors [76] via its trans-activating factor (Tat) [77]. The consequence is increased intracellular calcium flux, translocation of P-selectin (CD62P) from the alpha granules to the membrane surface, secretion of chemokine CD154, and release of platelet microparticles [77]. The process is by enhancing platelet NOX-2 oxidative stress [78].

9.2 Gut microbiol translocation

HIV preferentially infects CD4-T lymphocytes present in the gut leading to reduction in number and function [79]. The consequence is loss of gut epithelial immune protection and disruption of gut epithelial barrier allowing luminal indigenous intestinal bacteria to translocate out of the mucosa and into circulation [80]. Once in circulation, bacterial products such as lipopolysaccharides (LPS) interact with platelet toll-like receptors 4 (TLR4) [81]. The microbial products induce signal transduction mechanisms that eventually lead to facilitating platelet membrane receptor expression [82, 83]. The phenomenon of gut microbial translocation has been used to explain enhanced platelet reactivity despite therapy with antiplatelets such as ticagrelor in myocardial infarction [84]. However, some studies have disputed the role of LPS in platelet activation instead of reporting attenuation of receptor expression and aggregation in the presence of agonists [85] contradicting earlier findings. The paradoxical result may be due to the absence or presence of other factors such as soluble CD14 that prime TLR4 sensing of LPS [86], extent of TLR expression [87] or the different LPS isoforms [88], and experimental conditions [89] as well as clinical condition [89].

9.3 Immune complexes, cytokines, and inflammatory markers

9.3.1 Cytokines

HIV infection is associated with elaboration of cytokines from inflammatory cells, and these have been shown to induce platelet activation [90, 91]. The platelet activation is not limited to interleukins only, since tumor necrosis factor in blood leads to dose- and time-dependent increase in platelet expression of GPIIbIIIa, PS, and mitochondrial dysfunction [92]. The role of TNF-α in platelet activation and apoptosis are well supported by empirical evidence [93].

9.3.2 Immune complexes

Platelets express FcRIIA (CD32a) or simply FcR receptor that recognizes the constant region of IgG in immune complexes [94]. The consequence of platelet-immune
complex binding leads to platelet activation [95], aggregation and release of contents from alpha and dense granules [94], and microparticle formation [96]. The platelet activation from immune complexes is dependent on membrane GP IIbIIIa [97]. However, the immune complex-induced platelet aggregation is dependent on dose and charge [98].

Cross-reactive antibodies between HIV epitopes and platelet receptors have been described [99, 100].

9.3.3 Neutrophil extracellular traps (NETS)

When neutrophils encounter viruses such as HIV, they respond by releasing reactive oxygen species and net-like structures called neutrophil extracellular traps [101, 102]. The NETs, composed of DNA, histones, myeloperoxidase, citrullinated histones, and elastases, are the potent inducers of platelet aggregation and activation [103–105].

9.3.4 Platelet-leukocyte complexes

There is often cross-talk between platelets and leukocytes associated with bidirectional priming and activation of each other [106, 107]. These two cells interact through platelets such as P-selecti-PSGL-1, GPIb-vWF-CD18, integrin IIaIIb-fibrinogen-MAC-1 neutrophil linkages that lead to the formation of platelet-leukocyte aggregates (PLA) [108] linked by P-selectin-PSGL. These PLA conjugates have been found in HIV patients involving T-cells associated with CD42b and CD62P [109]. Elevated PLA together with other immune markers is positively correlated with increased platelet CD36, CD62P, and platelet aggregation but inversely with CD4 count [110].

9.3.5 vWF-GPIbα in platelet activation in HIV

There is evidence of endothelial damage [111] and increased vWF levels in HIV patients [66–68, 112, 113]. Apart from the high vWF Ag levels, of significant is the persistently high functionally active Ultralarge vWF multimers (ULvWFM) in HIV individuals [65] that causes adhesion even at low platelet counts [114]. Correspondingly, as HIV disease progresses, platelet expression of the integrin GPIbα decreases paradoxically unlike the other surface receptors indicating consumption [28].

9.4 Platelet apoptosis

There are similarities in markers of platelet activation and apoptosis [115]. In both processes, there is phosphatidylserine (PS) exposure on the membrane [116] and microparticles [117]. However, specific features of platelet apoptosis include mitochondrial membrane leakage characterized by changes in membrane depolarization ($\Delta\psi_m$) and increase in cytosolic caspases 3&8, [118, 119]. Indeed, features of platelet apoptosis and activation have been demonstrated in HIV patients [25, 32, 38]. It should be noted that the few studies demonstrating occurrence of full spectra of apoptosis in HIV individuals were confounded by cART viral suppression [32] and dengue co-infection [25] and therefore, whether results were specific to HIV in itself largely remains undetermined.
Some of the consequences of platelet apoptosis include thrombocytopenia [120, 121]. This is because, apart from the fact that apoptotic platelet eventually disintegrates [74], the surface exposure of PS acts as “eat me” signal for engulfment by the macrophages thus removing the altered cells from circulation shortening survival [122–124].

10. Antiretrovirals and platelet functions in HIV

Despite the success attained by cART in viral suppression and recovery of platelet counts [125, 126], their effects on platelet function remain variable. In general, platelet surface markers such as CD62P, PAC-1 and CD40L, soluble sCD62P, sCD40L as well as platelet-secreted chemokines such as RANTES persist despite cART viral suppression [27] with some variations between the individual drugs and study designs.

Platelet signal transduction and secretory effects are enhanced by HIV, but these effects are accentuated by cART. This was demonstrated by Pastori et al’s [78] study in which levels of sCD40L, platelet sNOX-dp, and 8-iso-PGF2α were elevated, the effects of PIs greater than NNRTI. The mechanism appears to be induction of oxidative stress, ROS, and arachidonic pathways that synergistically augment AA platelet activation. cART causes mitochondrial toxicities [127] via ROS release and inner membrane depolarization that eventually lead to apoptosis that persists even with viral suppression [32].

Abacavir is unique among cART [51] since it is a guanosine analogue and induces platelet activation via its effects on NO-cGMP signal transduction pathway [20]. In vitro, incubation of platelets with abacavir inhibits cAMP pathway and dose-dependently increases surface expression of P-selectin, an observation that is augmented by ADP agonist [128]. Compared with TDF and TAF, abacavir enhances platelet aggregation and increases agonist-induced platelet activation in vivo (CD62P, PAC-1) [31]. It has been shown that it induces both alpha and dense platelet granule secretions thereby increasing membrane CD62P [128] levels as well as increasing PAC-1 [129]. It also alters metabolic enzymes that lead to increase in PAF from leukocytes [130]. This likely explains its association with cardiovascular events where enhanced platelet hyperactivity plays a central role [131, 132].

Despite other studies reporting levels of platelets MP remaining unchanged [29] or increased [71] after initiating antiretrovirals, one study found MP TF levels decreased with cART treatment [133]. The difference could be attributed to monocyte phenotypes [134] and level of activation and attendant TF expression with cART [135]. This is because platelets undergo decryption [136] and transfer TF to monocytes using microparticles as vehicles [137, 138].

The effects of cART on platelets are complicated by other factors such as TNF-α, a known platelet activator and apoptosis inducer. Although TNF levels are often elevated in HIV infection, levels persist despite cART [139] even if used over 24-month period [34]. Whereas cART treatment decreases circulating bacterial LPS levels in HIV patients, platelet reactivity is increased instead [23] suggesting intrinsic effects of the drugs independent of bacterial translocation.

11. Antiplatelets in HIV/AIDS

People living with HIV/AIDS are at increased risk of cardiovascular events [140, 141], especially coronary heart disease [142, 143] and ischemic stroke [144, 145], than the
general population. The increased risk is due to HIV infection alone and accentuated by cART [146, 147].

Although there is evidence of enhanced platelet activation in association with HIV [27], studies of antiplatelet therapy in these patients have yielded inconsistent results, perhaps owing to drug interactions [148]. It should be noted that the studies so far done were on patients concurrently taking cART.

In a study of HIV-1 infected patients who had been on 6-month cART, it was found that 325 mg of oral aspirin-attenuated platelet aggregation to agonists, activation markers [37]. In the same study, although levels of urinary thromboxane were decreased in both HIV-positive cART untreated and treated, it was least responsive to aspirin. Furthermore, despite aspirin administration, suppression of platelet hyperactivity did not decline to baseline levels indicating the contributory effects of cART. Apart from the small sample size and short duration of therapy, other limitations of this pilot study are that it evaluated only one antiplatelet drug, and it did not perform subgroup analysis among the different cART drugs (NNRTI, PI, Raltegravir, and abacavir) as well as the racial and ethnic differences.

Although aspirin and R406 (thromboxane analogue) but not ticagrelor inhibits platelet engulfment, they do not inhibit CD62P expression or PMA complex formation [149]. Other studies have confirmed the suboptimal effects of aspirin on platelets agonist (collagen and epinephrine)-induced aggregation, surface expression of CD62P, CD40L, and PAC-1 from individuals with HIV taking ABC [53]. This study identified subjects taking abacavir-containing cART as poor responders. While cART is currently standard of care in the treatment of HIV, there are no data on effects of antiplatelets in PLWH before adoption of practice.

Clopidogrel reduces thrombogenicity and platelet hyperreactivity better than aspirin in PLWH on cART [21]. The question whether dual antiplatelet therapy compared to single agent may have a better reduction in platelet hyperreactivity in HIV concurrently taking cART was evaluated in the EVERE$^2$ST-HIV [18]. This study evaluated the extent of platelet inhibition patients with acute coronary patients on dual antiplatelet therapy undergoing PCI utilizing various platelet function assays [18]. The findings were that P2Y12 inhibitors (clopidogrel, prasugrel, and ticagralor) and aspirin were all associated with residual platelet reactivity on light transmission aggregometry (LTA), VerifyNow, and VASP assays. Furthermore, HIV infection was an independent risk factor for the high on antiplatelet reactivity that was increased by combined antiretroviral therapy (cART). Of the cART, protease inhibitors had greater effects than the NNRTIs. The residual platelet reactivity in PLWHIV despite viral suppression and dual antiplatelet therapy can probably be accounted by the active immune mechanisms and drug interactions [148].

Overall, few studies have evaluated the effects of antiplatelets in persons living with HIV. The available studies suffer from small sample sizes and have not been performed in populations not taking cART. Furthermore, the different classes of antiplatelets have not been evaluated. Of the studies done so far, the results do demonstrate neither efficacy nor improved outcomes with either aspirin or clopidogrel.

12. Conclusion

Infection with HIV is associated with reduced platelet count; extent of thrombocytopenia inversely correlates with viral load and disease progression. Despite thrombocytopenia, cardiovascular events are on the increase. There is associated
platelet hyperactivity, as evidenced by increased surface expression of CD62P, CD40L, platelet microparticles, and platelet leukocyte aggregates. There is enhanced secretion of chemokines such as RANTES. Combined antiretroviral drugs independently and synergistically with HIV enhance platelet hyperactivity that persists despite viral suppression. Data on the effects of antiplatelets in this population can at best be described as clinical equipoise.

Other declarations

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Future Opportunities and Tools for Emerging Challenges for HIV/AIDS Control

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