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REVIEW ARTICLE

HIV-associated thrombotic thrombocytopenic purpura (HIV-TTP): A practical guide and review of the literature

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Abstract

Background: Thrombotic thrombocytopenic purpura (TTP), a serious thrombotic microangiopathy (TMA), is prevalent in the South African HIV-infected population. The exact pathogenesis of HIV-associated TTP (HIV-TTP) is however still unclear with diagnostic and therapeutic inconsistancies.

Methods: A systematic review of the published literature regarding HIV-TTP was performed.

Results: HIV-TTP is still associated with significant morbidity and mortality in Africa despite the availability of anti-retroviral therpy (ART). Diagnosis of HIV-TTP requires the presence of a micro-angiopathic haemolytic anaemia with significant red blood cell schistocytes and thrombocytopenia in the absence of another TMA but background activation of the coagulation system and inflammation in HIV infected people can result in diagnostic anbiguity. Plasma therapy in the form of infusion or exchange is successful but expensive, associated with side-effects and not widely available. Adjuvant immunosuppression therapy may of benefit in patients with HIV-TTP and ART must always be optimised. Endothelial dysfunction caused by chronic inflammation and complement activation most likely contributes to the development of HIV-TTP.

Conclusion: The role of adjuvant immunomodulating therpy, the therapeutic targets and pathogenic contribution from endothelial dysfunction in HIV-TTP requires further investigation.

KEYWORDS
endothelial dysfunction, HIV, inflammation, management, thrombotic thrombocytopenic purpura

BACKGROUND

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy (TMA) associated with organ ischaemia and dysfunction. There is significant overlap between the different thrombotic microangiopathies, which also includes disseminated intravascular coagulation (DIC), in both pathogenesis and clinical presentation [1]. Secondary TTP can occur in relation to autoimmune diseases, such as systemic lupus erythematosus (SLE), chronic viral infections, notably HIV but also hepatitis and cytomegalovirus [1], and acute infections like coronavirus disease (COVID-19) [2]. Endothelial dysfunction and activation of the immune system are postulated to play pivotal roles in many of these varied conditions by promoting a hypercoagulable state [3–5]. Despite a significant amount of research on the role of endothelium in health and disease, a significant chasm still exits from 'bench to bedside' as far as endothelial biology is concerned, as is highlighted in the potential role of endothelial dysfunction in patients with HIV-associated TTP [6].

The microthromboses in TTP are initiated by the accumulation of von Willebrand factor (VWF), a coagulation factor produced and secreted by the endothelium. Ultra-large VWF (ULVWF) multimers accumulate in TTP because of an absolute or relative deficiency of the VWF cleaving protease, a-disintegrin-and-metalloproteinase-with-thrombospondin-motifs 13 (ADAMTS-13). Obstruction of the microvasculature by platelet-VWF microthrombi manifests as a haemolytic anaemia with red blood cell fragmentation and a significant thrombocytopenia. A diagnosis of TTP is made after exclusion of other forms of TMA [1].

Deficiency of ADAMTS-13 is either congenital, Upshaw–Schulman syndrome, or acquired in the background of conditions including malignancies, autoimmune diseases and infection, including HIV infection [1]. A relative deficiency of ADAMTS-13 may also occur with endothelial activation, damage and excessive release of ULVWF multimers manifesting as TTP-like syndrome, which occurs in the background of various disease processes [5]. This syndrome, in contrast to classical TTP, is mediated by complement activation with accumulation of proinflammatory C5b-9 membrane attack complexes (MACs), which form pores in endothelial cell membranes [5]. The resultant endotheliitis causes cellular apoptosis as well as activation of inflammatory pathways, which results in platelet activation and release of ULVWF multimers from endothelial stores. The platelet-rich VWF thrombi occlude the microcirculation in a process similar to TTP. There is some controversy as to whether similar pathogenic factors mediate HIV-associated TTP [7].

Vascular disease, including TMAs, related to endotheliitis is an established complication of HIV infection [8,9]. Endotheliitis, a state of endothelial cell dysfunction (ECD), is linked to a proinflammatory and procoagulant phenotype and occurs in patients with HIV infection, including virologically suppressed patients on antiretroviral therapy (ART) [8–10]. A full description of the mechanisms of endothelial damage related to HIV infection [11] is outside the scope of this review but these include chronic inflammation linked to ongoing HIV replication [12], opportunistic infections (including hepatitis C and *Mycobacterium tuberculosis*) with endothelial damage and metabolic dysregulation associated with ART. HIV proteins including trans-activator of transcription (tat), negative factor (nef) and membrane glycoproteins can damage endothelial cells, causing dysfunction and apoptosis [11]. Biomarkers of inappropriate endothelial cell activation and dysfunction are upregulated in HIV infection, including vascular adhesion markers, proinflammatory cytokines, chemokines and their receptors, coagulation factors and products of coagulation factor activation and breakdown [9,11].

PREVALENCE OF HIV-ASSOCIATED TTP

Thrombotic thrombocytopenic purpura was first described in HIV-infected cohorts in the 1980s [13,14]. The majority of these early cases occurred in men who presented with variable features of the diagnostic TTP pentad of fever, neurological and renal dysfunction, thrombocytopenia and microangiopathic haemolysis [13]. These patients showed significant heterogeneity in comorbid conditions and degree of immunosuppression although the patients treated with plasma therapy generally had good outcomes [14]. Limited investigation of the pathophysiology was, however, undertaken [14]. The relationship between HIV and TTP has been confirmed in multiple subsequent observational studies (Table 1).

Thrombotic thrombocytopenic purpura has declined in prevalence in HIV-infected patients in high-income countries [25]. This may reflect increased access to early suppressive ART. Conversely, TTP in low- and middle-income countries remains a significant cause of morbidity and mortality [21,23,24,26]. HIV-associated TTP was the commonest condition requiring therapeutic plasma exchange (TPE) provided by the South African National Blood Services (SANBS) with a calculated crude incidence of between 17.6 and 63.8 cases per million every year since 2011 [26]. This represents a considerable burden on healthcare resources, with many patients requiring admission and multiple cycles of TPE [21].

PATHOPHYSIOLOGY OF HIV-ASSOCIATED TTP

Classical TTP is caused by significantly reduced ADAMTS-13 activity either from birth or subsequent to the development of autoantibodies which are associated with a number of triggers, including infectious and autoimmune diseases as well as pregnancy [1]. The pathophysiological mechanism of TTP in HIV is not

TABLE 1 Observational studies of patients with HIV-associated TTP

Authors (year)	Study design	No. of HIV-infected patients with TTP	Study population and major findings
Becker et al. (2004) [15]	Multicentre cohort study over 6 years	17[a]	• TMA associated with lower mean $CD4^+$ T-cell count, higher mean viral load • Comorbidities reported – *Mycobacterium avium* and hepatitis C virus
Miller et al. (2005) [16]	Single centre cohort study over 6 years	8	• 6 patients with decreased ADAMTS-13 and 1 with autoantibodies • Good response to TPE and ART
Novitsky et al. (2005) [17]	Single centre cohort study over 7 years	21 (23 HIV uninfected controls)	• HIV infected patients with TTP respond to FFP infusion quicker than HIV uninfected patients • None of the patients with HIV-associated TTP required TPE • HIV-associated microangiopathy is highly responsive to plasma infusions
Gunther et al. (2007) [18]	Single centre cohort study over 3 years	22 (3 HIV uninfected controls)	• HIV-infected patients with TTP – increased median D-dimer but normal coagulation factor assays • Lower platelet counts and haemoglobin levels compared with HIV-uninfected patients with TTP
Malak et al. (2008) [19]	Multicentre prospective cohort study	29	• 17 (58%) significantly decreased ADAMTS-13 levels; 12 (42%) with detectable ADAMTS-13 activity • Mortality in HIV-associated TMA correlated with higher ADAMTS-13 and VWF levels
Hart et al. (2011) [20]	UK TTP registry over 10 years	24	• TTP was HIV index presentation in 30% • Poor adherence to ART associated with relapse in 4 patients • Responds to TPE and ART $\pm$ steroids; Immunomodulator (e.g. rituximab) needed in 10% • Duration of TPE correlated with viral load • ADAMTS-13 activity <5% in all patients and anti-ADAMTS-13 antibodies in 80%
Masoet et al. (2017) [21]	Single centre experience over 5 years	40 (12 HIV uninfected controls)	• Overall mortality rate: 44.2% • ART associated with better outcomes • Clinical: fever commoner in HIV infected patients; neurological pathology was common in both groups • 90.2% of HIV-infected patients with TTP only received plasma infusion with good clinical response
Bade et al. (2018) [22]	Single centre experience over 12 years	28	• Median viral load: 89 500 copies/mL • Median $CD4^+$ T-cell count: 58 cells/μL with good response to TPE
Louw et al. (2018) [23]	Single centre experience over 2 years	16	• TTP was HIV index presentation in 2 (13%); 14 (87%) patients had variable virological control on ART • Female preponderance (female:male ratio: 4:1) • TPE for median of 12 days with 96.5% survival
Swart et al. (2019) [24]	Single centre experience over 5 years	41	• TTP was index presentation of HIV in 78% of patients • Median of 10 days TPE • Relapse rate of 9.8%; mortality rate of 29.3%

Abbreviations: ADAMTS-13, a-disintegrin-and-metalloproteinase-with-thrombospondin-motifs 13; ART, anti-retroviral therapy; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; TMA, thrombotic microangiopathy; TPE, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura; UK, United Kingdom.

[a]TTP and haemolytic uraemic syndrome (HUS).

entirely clear, with variable levels of both ADAMTS-13 and associated autoantibodies creating diagnostic uncertainty [7,27,28]. It is still unclear whether a one- or two-hit model is operational in the pathophysiology of HIV-associated TTP but work by Feys et al. [29] in a primate animal model demonstrated that functional, *in vivo* inhibition of ADAMTS-13 was sufficient to induce development and phenotypic expression of TTP in the absence of a second trigger.

A number of secondary triggers for HIV-associated TTP have been proposed. Multiple opportunistic infections including hepatitis C, cytomegalovirus, Kaposi sarcoma herpesvirus and *Mycobacterium tuberculosis* may directly activate and damage the endothelium, resulting in release of ULVWF multimers [19,22,30]. Underlying endotheliitis, associated with inflammation, is present in both ART virally suppressed and ART-naïve HIV-infected patients [3,10,31,32]. Endothelial dysfunction in HIV-associated TTP has been proposed as the major driver of microvascular disease, with studies showing a direct impact of HIV proteins on endothelial cells [33,34]. Recently, the contribution of other innate effectors, including complement, has also been highlighted, particularly in the related TMA, TTP-like syndrome [5]. Complement, a zymogenic cascade which assembles on cell membranes, can mediate loss of endothelial cell integrity and endothelial cell apoptosis [35]. Complement activation, commonly associated with HIV infection [36], also causes platelet activation and recruitment of leukocytes to the site of inflammation, resulting in the development of immunothrombosis which may present as a TMA [37].

CLINICAL AND LABORATORY PRESENTATION OF HIV-ASSOCIATED TTP

Initial guidelines for the diagnosis of congenital or acquired TTP defined a diagnostic pentad of fever, haemolytic anaemia, cutaneous (purpura) or other bleeding related to thrombocytopenia, neurological abnormalities and renal dysfunction [30]. Currently, the combination of thrombocytopenia with a microangiopathic anaemia with features of haemolysis [elevated lactate dehydrogenase (LDH), reduced haemoglobin and haptoglobin, with increased red blood cell (RBC) fragments] is sufficient for a presumptive diagnosis of TTP [38]. The differential diagnosis of TTP and TTP-like syndrome includes other TMAs, most importantly DIC. The distinction can be challenging because of the significant overlap of clinical and laboratory test results between the syndromes [30]. Correct diagnosis is essential, however, in order to ensure appropriate treatment [30]. As TTP is a diagnosis of exclusion, it is important to investigate the patient for other contributory conditions, including autoimmune disease, malignancy and infection [1]. Given the need to treat TTP urgently, these investigations are frequently conducted after initiation of therapy (Table 2).

The clinical and laboratory presentation of patients with HIV-associated TTP is heterogeneous [7]. Observational studies report varying incidences of neurological dysfunction, fever and renal failure, with neurological dysfunction and fever being prominent in certain cohorts described in South Africa [17,21,23,24]. Cardiac ischaemia has been described in up to 25% of patients with TTP and the measurement of troponin levels may be of value in patients presenting with HIV-associated TTP [1]. Although thrombocytopenia and evidence of microangiopathic haemolysis (particularly elevated LDH levels) are invariably present during the course of disease [23,24], other laboratory findings may be atypical. D-dimer levels are often raised and there may be variable activation of the coagulation pathways [18,23]. Patients with HIV-associated TTP respond to TPE but may not achieve full normalization of parameters because of the presence of dyshaematopoiesis, with persistence of thrombocytopenia and anaemia [39,40]. Viral load and CD4 T-cell count show an inconsistent relationship with diagnosis and prognosis. Although TTP is more common in patients with poor virological control, it may present in patients with viral suppression [22-24,28]. ART non-compliance is nevertheless associated with TTP relapse [7,20,21,41]. A full list of recommended investigations at our centre is included in Table 2.

Clinical predictive scores, such as the PLASMIC [platelet count, haemolysis, active cancer, mean RBC volume (MCV), international normalized ratio (INR) and creatinine] score [42], have been developed to assist in the diagnosis of TTP (Table 3). The PLASMIC score is based on clinical and routine laboratory parameters and predicts the likelihood of severe ADAMTS-13 deficiencies in patients with a TMA. The utility of this score requires validation in patients with TTP in whom ADAMTS-13 deficiency does not drive pathogenesis such as patients with TTP-like syndrome [5,7,28,42].

TREATMENT OF TTP AND TTP-LIKE SYNDROME

HIV-TTP is treated either with daily therapeutic plasma exchange (TPE) or with plasma infusion [1,17–19,35,39]. TPE removes and dilutes ULVWF multimers, autoantibodies and inflammatory cytokines while supplementing

TABLE 2 Recommended baseline laboratory investigations

Test parameter	Expected findings
Full blood count (FBC) with manual smear review	Reduced Hb (concentration frequently < 7 g/dL) with > 10 RBC fragments per high-power field and marked thrombocytopenia (PLT count < 20×10^9/L)
Lactate dehydrogenase (LDH)	Significantly elevated (frequently > three times upper limit of normal)
End-organ damage • Kidney dysfunction (U&E) • Cardiac injury (troxponin T)	U&E generally unremarkable Underlying cardiac muscle injury has been described
Liver function test (LFT)	Unconjugated bilirubinaemia Elevated aspartate transaminase (AST)
Disseminated intravascular coagulation (DIC) screen (PT, fibrinogen, D-dimers and platelet count)	PT: preserved or mildly prolonged Fibrinogen: variable (may be elevated as acute-phase response) D-dimers: often significantly elevated Platelet count: frequently < 20×10^9/L
HIV serology/viral load/CD4$^+$ count	HIV serology: usually positive Viral load: often high CD4 T-cell count: variable
Direct antiglobulin test (DAT)	IgG and C3d variable
Haptoglobin	Usually undetectable
Possible additional triggers to consider in appropriate patient groups	
Infections	*Mycobacterium tuberculosis* – sputum (Gene Xpert® and microscopy), chest X-ray, urine and blood culture Gram-negative organisms including *Shigella* spp. and *E. coli* spp. (to exclude HUS) – bacterial culture Viral infections with endothelial cell activation/tropism including Gamma herpesviridae, hepatitis B and C – serology and viral PCR testing
Malignancy	B-cell lymphoma (lymph node biopsy, bone marrow biopsy)
Pregnancy	Beta-HCG
Autoimmune disease	Rheumatoid factor Anti-nuclear factor Anti-double-stranded DNA
Therapeutic monitoring to guide plasma therapy	
FBC and differential count	Therapeutic targets: Platelet count should be sustained above 150×10^9/L for 2 days (may not fully normalize); Scanty red cell fragments; Recovery of Hb to > 6 g/dL.
LDH	Should show a persistent downward trend and ideally be < 450 U/L (may not fully normalize)
Calcium, magnesium and phosphate	To exclude metabolic abnormalities associated with plasma therapy and citrate anticoagulation

Abbreviations: DNA, deoxyribonucleic acid; FBC, full blood count; Hb, haemoglobin; HCG, human chorionic gonadotropin; HUS, haemolytic uraemic syndrome; IgG, immunoglobulin G; PCR, polymerase chain reaction; PLT, platelet; PT, prothrombin time; RBC, red blood cells; U&E, urea and electrolytes.

ADAMTS-13 [1,41]. TPE is, however, invasive and not available in all centres [26]. Infusion of fresh frozen plasma (FFP) alone (at a dose of 30 mL/kg per day) has been shown to be efficacious in the treatment of HIV-TTP and dilutes ULVWF multimers while supplementing ADAMTS-13 [17]. Plasma infusion can, however, result in the administration of insufficient amounts of plasma due to ensuing fluid overload and unavailability of FFP, resulting in poor therapeutic responses and a need to convert to TPE [17]. In HIV-infected patients, it may be difficult to achieve a normal platelet count [39], and LDH levels or schistocyte numbers may be a more appropriate target. Methods for the quantification of schistocytes are poorly standardized, however, and usually rely on subjective

TABLE 3 PLASMIC score for the prediction of thrombotic microangiopathy associated with severe a-disintegrin-and-metalloproteinase-with-thrombospondin-motifs 13 (ADAMTS-13) deficiency with high probability of thrombotic thrombocytopenic purpura (TTP) [42]

Parameter	Points
Platelet count < 30 × 10^9/L	1
Haemolysis: reticulocyte count > 2.5% or haptoglobin undetectable or elevated indirect bilirubin	1
No active cancer	1
No history of solid organ or stem cell transplant	1
Mean red blood cell volume (MCV) < 90 fL	1
International normalized ratio (INR) < 1.5	1
Creatinine < 176.8 µg/dL	1
• Score of 0–4: low risk of severe ADAMTS-13 deficiency • Score of 5: intermediate risk of severe ADAMTS-13 deficiency • Score of 6–7: high risk of severe ADAMTS-13 deficiency	

peripheral blood smear examination [43]. In the experience of the authors, LDH is an objective, reliable surrogate marker of haemolysis. TPE is expensive, requires large volumes of FFP, has the risk of citrate-related reactions and is not widely available in many low-income countries [26]. Furthermore, administration of FFP may have significant immunological and non-immunological adverse effects, including transfusion-associated circulatory overload, transfusion-associated lung injury and allergic responses [44]. The insertion of a large-bore catheter can result in vessel injury and predispose to thrombosis and bleeding. Drip site sepsis is another complication of indwelling intravenous catheters [45]. For these reasons, TPE should be discontinued as soon as clinically appropriate.

Although ART has an inconsistent effect on the development of HIV-associated TTP [23,24], it most likely prevents TTP relapse [7,20,21]. For this reason, ART should be initiated as soon as possible. A theoretical concern is the development of TTP following initiation of ART as an immune reconstitution inflammatory syndrome (IRIS), although haematological manifestations in IRIS are uncommon and there are no reports of TTP as IRIS in the literature [46].

The role of adjunctive treatments in HIV-associated TTP is unclear. Immunosuppression, including oral steroid therapy, is used sporadically to reduce inflammation-associated endotheliitis [7,41]. Corticosteroids are frequently employed to treat inflammation and autoimmune diseases based on their action on numerous steps in the inflammatory pathway [47,48]. Other therapies that have been employed include the anti-CD20 monoclonal antibody, rituximab, which may assist in reducing levels of autoantibodies against ADAMTS-13 [20,25,30]. However, a local study in South Africa to investigate the pathophysiological significance of ADAMTS-13 autoantibodies in HIV-TTP patients demonstrated that these antibodies were present in HIV-infected people without TTP and the exact clinical relevance remains unclear [28]. Novel therapies are in development but clinical trials focus on patients with congenital, relapsing and refractory classic TTP [30]. The monoclonal antibody caplacizumab, for example, is a humanized anti-VWF antibody which prevents platelet aggregation [49]. Although approved for TTP therapy in patients with acquired and congenital forms of the disease, no wide-scale studies have investigated its role in HIV-associated TTP [49]. Another potential avenue of exploration, is the role of complement inhibition in HIV-associated TTP syndrome, which may share a common pathogenesis with TTP-like syndrome [5]. Eculizumab, a monoclonal antibody which inhibits formation of the membrane attack complex, assists in prevention of thrombosis in paroxysmal nocturnal haemoglobinuria and may have a similar effect in TTP-like syndrome [5].

CONCLUSIONS

HIV-related TTP was relatively common prior to widespread access to ART, implying that viral replication drives pathogenesis [1,25,41,50]. Local African case series and investigational studies, however, suggest that HIV-associated TTP is still prevalent and occurs at a range of viral loads in ART-treated and -untreated patients [18,21,23,24,26,32]. ADAMTS-13 levels in these local and some international cohorts have also been variable, with an absence of inhibitory antibodies in many patients suggesting a different pathophysiology in HIV-associated, acquired TTP compared with other forms of secondary TTP [7,20,27,28]. Endothelial dysfunction with excessive release of VWF which overwhelms ADAMTS-13 proteolytic capacity has been postulated as a pivotal initiating event in HIV-associated TTP [19,25]. Infection with HIV is associated with endothelial dysfunction, which has been described extensively in the literature, and the causes include direct viral effects, the effects of opportunistic infections and inflammation including complement activation [3,9,32].

Investigation of HIV-associated TTP should include a haemolytic work-up, measurement of ADAMTS-13 levels and autoantibodies directed against ADAMTS-13 [19]. Coagulation parameters may show abnormalities [18], and other triggers (infectious and non-infectious) should be actively excluded [1]. Red cell fragments, LDH levels and platelet count are useful in monitoring therapeutic response [1,23].

Standard-of-care remains daily TPE or plasma infusion [1,17]. The applicability of international treatment regimens and the duration and target end-point of TPE require further investigation, especially in the context of thrombocytopenia being a common finding in HIV-infected patients without TTP [39]. Adjunctive therapy with immunosuppressants and novel agents shows some benefit in small case series [1,20]. Initiation and optimization of ART remains central to preventing TTP relapse in these patients [20,21,41].

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CONFLICT OF INTEREST

SL, BFJ, TMW, ZC and ESM declare there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

SL and ESM – devising concept, literature selection and review, analysis and drafting manuscript; BJ, TW and ZC – drafting of manuscript and critical reading of manuscript.

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