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Presentation of HIV-associated thrombotic thrombocytopaenic purpura and response to plasma exchange: a 10-year retrospective single-centre experience

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Declaration

I, Sayuri Harishun, declare that this research report is my own, unaided. It is being submitted for the degree of Master of Medicine in the branch of Internal Medicine at the University of Witwaterstrand. It has not been submitted before for any degree or examination at this or any other university.

Signed *Sayuri Harishun*.

Acknowledgements

The support of Dr Davies and Dr Cassimjee have been instrumental in the successful completion of this research project and is gratefully acknowledged.

Ethical considerations

Permission for this retrospective study was obtained from Dr Bayat (Head of Department of Internal Medicine, Helen Joseph Hospital), Department of Nephrology Helen Joseph Hospital, Research committee Helen Joseph Hospital, South African National Blood Services, and the Ethics Committee of the University of the Witwatersrand (clearance number M201166).

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Abstract

Background

HIV is an important cause of thrombotic thrombocytopenic purpura (TTP) in the local context. The presentation, mortality, and renal outcomes of HIV-associated TTP (HIV-TTP) remain poorly characterized, and the role of plasma exchange (PEX) as a treatment strategy is largely unreported.

Methods

We retrospectively reviewed 105 cases of HIV-TTP treated with PEX between 1/1/2010 – 31/12/2020. The presentation, and mortality and renal outcomes of this cohort are described, and complications of PEX therapy are characterised. The effect of HIV infection severity on HIV-TTP presentation, and the effect of both these parameters on mortality, PEX complications, and renal outcomes are analysed using appropriate regression models.

Results

There is an association between advanced HIV infection and HIV-TTP and there is a predilection for young Black women. Neurological deficit is a common presenting feature. Severity of HIV infection may influence renal dysfunction at presentation; this in turn may affect survival outcomes on PEX as may choice of plasma infusant. HIV-TTP carries significant mortality risk; sepsis is a notable contributor to mortality in HIV-TTP treated with PEX. Residual renal impairment is uncommon in the survivors of HIV-TTP.

Conclusions

Mortality remains high in HIV-TTP treated with PEX, and sepsis-related complications are of concern. Randomized prospective studies are required to evaluate the use of PEX versus plasma infusion (PI) and infusant choice in HIV-TTP. Longer duration follow-up studies are needed to evaluate residual renal impairment in survivors of HIV-TTP.

Introduction

The thrombotic microangiopathies are a heterogenous group of rare disorders with an estimated annual incidence of 4 cases per million population in the developed world.[1] Data from the developing world is lacking, reflecting the difficulty of accurate diagnosis. However, the South African National Blood Services (SANBS) have recently estimated an annual incidence rate of 17.6 – 63.8 cases per million population through analysis of plasma exchange (PEX) prescribing patterns.[2]

This increased incidence appears to reflect the significant contribution of HIV as a causative factor for thrombotic thrombocytopenic purpura (TTP) spectrum Thrombotic microangiopathies (TMAs) in the local context. Previous South African case series have suggested that 77 – 79% of patients diagnosed with TTP comprise people living with HIV (PLWH),[3 – 5] and HIV is disproportionately represented as a cause of TTP in case series from regions with lower HIV seroprevalence rates.[6]

Pathophysiological mechanisms underlying the development of TTP-HIV have yet to be fully elucidated and may vary between patients. Endothelial dysfunction arising directly from cellular infection by the virus [7] or indirectly as a result of cellular injury from shed viral proteins and the chronic inflammatory milieu which accompanies HIV infection may precipitate the disorder in some patients.[8] In other patients, immune dysregulation associated with HIV infection may result in the development of autoantibodies to ADAMTS13 (*a d*isintegrin *a*nd *m*etalloproteinase with a *t*hrombo*s*pondin type 1 motif, type *13*), an enzyme which cleaves ultra-large von Willebrand factor (UL-vWF) to exert an antithrombotic effect. [9] This variation in pathophysiological mechanisms in HIV-TTP may account for lack of universally detectable ADMATS13 deficiency or inhibitor levels in patients diagnosed with the disorder.[9]

TTP is almost universally fatal without treatment; use of PEX reduces mortality to below 10%. [10] PEX has been reported to offer superior survival outcomes over plasma infusion as sole treatment;[11] this benefit of PEX is believed to derive from additive removal of UL-vWF and autoantibody if present, as well as ameliorating risk of fluid overload associated with high-dose plasma infusion.[12] Mortality in HIV-TTP has been reported as higher than that in other forms of the disorder, possibly

reflecting increased risk of treatment-related sepsis in advanced HIV infection which is characteristic of this presentation.[13]

Long-term sequalae of TTP remain generally poorly reported. Up to 45% of TMA survivors may manifest new-onset hypertension, with 21% demonstrating chronic kidney disease (CKD) in the form of reduced estimated glomerular filtration rate (eGFR) and up to 18% requiring ongoing dialytic support.[14] Although TTP has been suggested to be an important cause of acute kidney injury (AKI) in South Africa in PLWH,[15] characterisation of long-term renal outcomes in survivors of HIV-TTP is lacking.

High HIV seroprevalence rates in sub-Saharan Africa [16] contribute to the increased incidence of TTP reported in the local context and mandate better characterization of the disorder and of the treatment and outcomes thereof. We therefore analysed the largest cohort of HIV-TTP yet reported from Africa to describe the presentation, responsiveness to PEX and complications thereof, and long-term renal outcomes of the disorder.

Methods

A retrospective analysis of all patients receiving plasma exchange (PEX) for treatment of presumed HIV-associated thrombotic thrombocytopenic purpura (HIVTTP) at our institution during the period 1 January 2010 – 31 December 2020 was performed. Inclusion criteria used for this study was all HIV positive patients with TTP over the age of 18 who received plasma exchange. The following patients were excluded from this study:

1. All patients younger than 18 years of age.
2. Patients with incomplete or missing data.
3. All patients where retrospective review suggests the possibility of a cause of TTP other than HIV infection, including:

• Patients where retrospective review suggests the possibility of an underlying autoimmune diagnosis as indicated by a positive serological test or contemporaneous clinical features, including SLE, scleroderma, and antiphospholipid syndrome.

• Patients where retrospective review of contemporaneous clinical and laboratory data indicates the possibility of an underlying haematological or solid organ malignancy.
• Patients who are retrospectively documented to have been pregnant at the time of presentation.
• Patients where retrospective review indicates the possibility of disseminated intravascular coagulopathy (DIC) as indicated by increased INR (greater than 1.4) or decreased antithrombin III level.
• Recipients of haemopoietic or solid organ transplants.
• Patients retrospectively found to have been prescribed drugs that are known to cause TTP such as (clopidogrel, quinine, ticlopidine, calcineurin inhibitors, chemotherapy).

Standard treatment for HIV-TTP at this institution is daily PEX using fresh frozen plasma (FFP) or cryosupernatant plasma until remission is achieved as indicated by improvement of lactate dehydrogenase (LDH) activity to below 200 IU/mL and platelet count to above 140 x 10^9/mm^3.[17] Hydrocortisone 50mg daily 30 minutes before PEX is additionally prescribed with paracetamol and promethazine to reduce risk of anaphylactic reaction during treatment; immunosuppression is reserved for those patients who fail to respond to PEX.[17] All patients additionally receive emergent initiation of antiretroviral therapy (ARV).

Patients were identified from the South African National Blood Services database and from clinical records. Diagnosis of HIV-TTP was retrospectively confirmed as recommended by the presence of microangiopathic haemolysis (anaemia with peripheral blood schistocytes, and increased serum LDH activity above 190 IU/mL) and thrombocytopenia (platelet count below 140 x 10^9/mm^3) with international normalised ratio (INR) below 1.5 and no other cause evident.[5],[17],[19] Since the PLASMIC score is unvalidated for TTP categories which do not feature ADAMTS13 deficiency,[8] this system was not used to retrospectively confirm the diagnosis of HIV-TTP in this series. The PLASMIC score was developed by the Harvard TMS Research Collaborative. [20] It is used for estimating the likelihood of severe ADAMTS13 deficiency in adults with suspected TTP. [20] The parameters included in the score is the patients platelet count, features of haemolysis, if the patient was treated for cancer in the past year, a history of solid-organ or stem-cell transplant, the

mean corpuscular volume, the international normalized ratio and the creatinine result. [20] Pregnant women, patients with positive autoimmune serology, and those diagnosed with malignancy were excluded from analysis. Since institutional resource limitations preclude routine measurement, ADAMTS13 activity was not included as a diagnostic parameter in this series. A total of 101 patients presenting with 105 episodes of HIV-TTP were included in the final analysis.

Anonymised data detailing the demographics and HIV-related disease status of affected patients, the clinical and laboratory features of their disease presentation, the nature and volume of plasma infusant prescribed, their response to PEX, and kidney function at subsequent follow-up was obtained from medical archives and saved in a secured Excel database prior to export to Stata© version 17 (StataCorp LLC, College Station, Texas, USA) for analysis.

Demographics, HIV-related disease status, and presentation of HIV-TTP were characterised for the cohort. Presentation of HIV-TTP was compared between Centres for Disease Control (CDC) stages of HIV infection using Pearson Chi-square or Kruskall Wallis ANOVA testing as appropriate and the effect of HIV viral load on presentation analysed using the Spearman rank order test. Factors affecting inpatient mortality during PEX treatment were modelled using Cox proportional hazards, ascribed aetiologies of inpatient death were also characterised as were complications of PEX. Factors affecting the development of complications of treatment were modelled using logistic regression. Residual kidney dysfunction as evidenced by estimated glomerular filtration rate (eGFR) was determined for all survivors at discharge and for those survivors completing at least 2 months of outpatient follow-up on discharge; in the latter group factors affecting renal function at follow-up were modelled using linear regression analysis.

Permission to undertake this study was obtained from the University of the Witwatersrand Human Ethics Research Committee (protocol number M201166); the study was undertaken in accordance with the principles of the Declaration of Helsinki.

Results

A total of 105 separate episodes of HIV-associated thrombocytopenic purpura (HIVTTP) occurred in 101 patients during this study; recurrences were documented in 4 patients. Demographic characteristics; CD4 count, HIV viral load, and antiretroviral (ARV) therapy; and features on presentation of patients with HIV-TTP are shown in table 1.

Table 1. Demographics and presentation of patients diagnosed with HIV-TTP

n (%) or median (interquartile range)

Age (years)	35 (32 – 43)
Sex	
Female	66 (65.3%)
Male	35 (34.7%)
Ethnicity	
Black African	95 (94.1%)
Non-black	6 (5.9%)
CD4 count ($x10^6/mm^3$)	146 (78 – 291)
Viral load (copies/mL)	120800 (899 – 789000) 6
Viral load suppression (< 20 copies/mL)	(5.7%)
CDC stage*	
Stage 1	7 (6.7%)
Stage 2	34 (32.4%)
Stage 3	64 (60.9%)
On antiretroviral therapy	23 (21.9%)
On ARV therapy longer than 6 months	16 (15.2%)
Interrupted ARV therapy prior to	26 (24.8%)
admission	56 (53.3%)
Newly diagnosed HIV positive	

Main indication for presentation	
Neurological deficit	
Confusion	55 (52.4%)
Focal neurology / seizures	6 (5.7%)
Headache	2 (1.9%)
Haemorrhagic	
Bleeding	22 (20.9%)
Anaemia symptoms	13 (12.4%)
Petechiae	4 (3.8%)
Other	
Non-specific abdominal	2 (1.9%)
Fever	1 (0.9%)
Objective pyrexia	8 (7.6%)
Temperature (^{o}C)	36.2 (36.1 – 36.3)
Neurological deficit	77 (73.3%)
Haemoglobin (g/dL)	6.6 (5.6 – 8.2)
LDH (IU/mL)	1130 (783 – 1880)
Red cell fragmentation	
1+	3 (2.9%)
2+	23 (21.9%)
3+	79 (75.2%)
Platelet count (x10^9/mm^3)	15 (12 – 21)
Creatinine (µmol/L)	109 (78 – 157)
eGFR (mL/min/1.73m^2)	55 (32 – 77)

Centres for Disease Control (CDC) stages: Stage 1: CD4 count ≥ 500 cells/mm^3 without other AIDS-defining illness; Stage 2: CD4 count 200 – 500 cells/mm^3 without other AIDS-defining illness, Stage 3: CD4 count < 200 cells/mm^3 of the presence of an AIDS-defining illness

Red cell fragmentation 1+: slight/few, 2+: moderate, 3+: marked

Presentation with HIV-TTP was associated with advanced HIV infection and was the index diagnosis of HIV in 53.3% of patients. Amongst 46 PLWH prior to diagnosis of HIV-TTP, 26 (53.1%) had interrupted ARV therapy, and less than a third (16 patients,

32.6%) had been prescribed ARV for more than 6 months prior to presentation. Reflecting this, the bulk (60.9%) of patients had advanced HIV infection as evidenced by CDC stage, and only 6 patients (5.7%) had an HIV viral load below detectable limit at presentation.

Neurological deficits were the leading initial indication for presentation, accounting for 63 cases (60%); neurological deficit was additionally recorded in 14 patients with initial presentation for haematological manifestations for TTP. Confusion was the most commonly encountered form of neurological deficit (55 cases), followed by focal neurology (6 cases) which comprised seizures (3 cases), hemiplegia (2 cases), and acute loss of consciousness (1 case). Haemorrhagic manifestations of thrombocytopenia were the next most common indication for initial admission (39 cases, 37.1%). Active bleeding was the most frequent haemorrhagic complication (22 cases), comprising 10 cases of epistaxis, 4 cases of spontaneous / easy bruising, 3 cases of gum bleeding, 2 cases each of haematemesis and vaginal bleeding, and one case of melena stool.

No difference was detected in presenting objectively recorded neurological deficit, temperature, haemoglobin concentration, LDH activity, qualitative red cell fragmentation, platelet count, or creatinine or eGFR between CDC stage (table 2).

Table 2. Presenting features of HIV-TTP compared between CDC stages

	CDC stage 1 (n = 7)	**CDC stage 2 (n = 34)**	**CDC stage 3 (n = 64)**	**P**
Neurological deficit	5 (71.4%)	24 (70.6%)	48 (75%)	0.889
Temperature (ºC)	36.3 (36.3 – 36.4)	36.2 (36.1 – 36.4)	36.2 (36.1 – 36.3)	0.336
Haemoglobin (g/dL)	6.8 (6.3 – 8.3)	7.1 (5.5 – 8.3)	6.2 (5.5 – 7.9)	0.551
LDH (IU/mL)	1200 (910 – 1824)	1094 (824 – 1958)	1106 (730 – 1868)	0.975

Red cell fragments				0.648
1+	0	0	3 (4.7%)	
2+	1 (14.3%)	7 (20.6%)	15 (23.4%)	
3+	6 (85.7%)	27 (79.4%)	46 (71.9%)	
Platelet count (x 10^9/mm^3)	15 (14 – 28)	13 (12 – 19)	16 (12 – 21)	0.325
Creatinine (µmol/L)	86 (64 – 150)	102 (71 – 135)	113 (84 – 175)	0.197
eGFR (mL/min/1.73m^2)	66 (45 – 115)	63.5 (37 – 78)	50 (29.5 – 72.5)	0.253
Variables are n (%) or median (interquartile range); p, Pearson Chi-square or Kruskall Wallis ANOVA, as indicated.				

No difference was similarly detected in HIV viral load (HIVVL) between those patients with neurological deficit and those without, or between qualitative red cell fragmentation groups. No correlation was observed between HIVVL and presenting haemoglobin concentration, LDH activity, or platelet count. A significant correlation was however detected between HIVVL and presenting serum creatinine and eGFR (table 3).

Table 3. Association between HIV vial load and presentation of HIV-TTP

Objectively recorded neurological deficit

	Neurological deficit	**No neurological deficit**	**P**
HIVVL	144560 (7025 – 784250)	65000 (247 – 1330000)	0.360

Qualitative red cell fragments

	1+	**2+**	**3+**	
HIVVL	386 (32 – 2320000)	133000 (899 – 768000)	69900 (8530 – 840000)	0.785

Haemoglobin concentration, LDH activity, platelet count, serum creatinine

	R_2	**P**
Haemoglobin (g/dL)	0.02	0.849
LDH (IU/mL)	0.06	0.561
Platelet count (x10^9/mm^3)	0.02	0.855
Creatinine (µmol/L)	0.28	0.004
eGFR (mL/min/1.73m^2)	-0.28	0.005

Values are median (interquartile range); P, Mann Whitney U or Kruskall Wallis ANOVA, as appropriate; $R^{2,}$ as determined by Spearman Rank Order correlation

Fifty-six cases (53.3%) were treated using FFP as plasma substitute, 34 (32.4%) received cryosupernatant plasma; the remaining 15 cases received a combination of FFP and cryosupernatant plasma. A median of 9 daily PEX sessions were needed to achieve remission in survivors of HIV-TTP (interquartile range 5 – 15 exchanges). CDC stage (P = 0.599), HIV viral load (P = 0.238), presenting haemoglobin concentration (P = 0.874), platelet count (P = 0.993), LDH activity (P = 0.862), eGFR (P =0.842), and choice of infusant (P = 0.421) did not appear to affect the duration of PEX needed to achieve remission amongst survivors.

Forty-eight patients demised on PEX during the course of this study; the inpatient mortality rate in this study was thus 45.7%. Death was ascribed to HIV-TTP in 34 cases (72.3% of mortalities) with one additional patient dying as a result of an intracranial bleed likely precipitated by TTP-related thrombocytopenia. Sepsis accounted for 12 deaths (25.5% of mortalities); death resulting from sepsis was not associated with CDC HIV infection stage (OR 0.561, 95% CI 0.20 – 1.56, P = 0.270). Use of FFP as infusant was associated with increased risk of mortality in Coxproportional hazards modelling (table 4, figure 1); better preserved renal function at presentation reduced risk of dying.

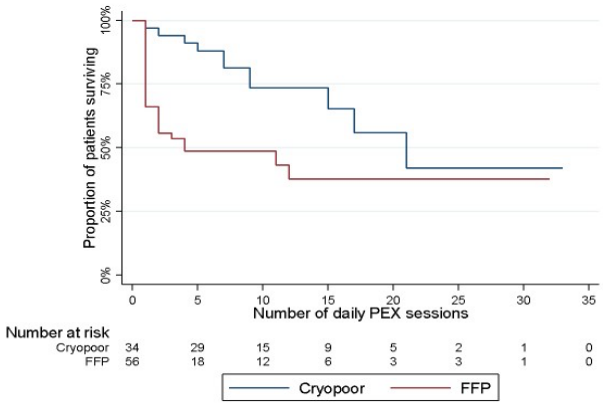
Table 4. Factors affecting risk of inpatient mortality during PEX treatment

	HR (95% CI)	**P**
Increasing age (years)	0.97 (0.93 – 1.01)	0.096
Female sex	0.95 (0.46 – 1.97)	0.890
Use of FFP as infusant	2.87 (1.32 – 6.22)	0.008
CD4 count ($x10^6/mm^3$)	0.99 (0.99 – 1.00)	0.300
HIV viral load (copies/mL)	1.00 (1.00 – 1.00)	0.074
Presence of neurological deficit	1.54 (0.64 – 3.72)	0.332
Haemoglobin (g/dL)	0.99 (0.81 – 1.22)	0.982

LDH (IU/mL)	1.00 (0.99 – 1.00)	0.288
Platelet count (x10^9/mm^3)	0.99 (0.97 – 1.03)	0.959
eGFR (mL/min/1.73m^2)	0.97 (0.96 – 0.99)	0.001

HR, hazard ratio; CI, confidence interval

Figure 1. Kaplan Meier survival analysis by plasma infusant



The Kaplan Meier survival analysis by plasma infusant showed the use of FFP as infusant was associated with increased risk of mortality. There is a marked difference in survival at day 5 of PEX sessions noted between the cryopoor and FFP groups.

Complications of PEX were recorded in 42 treatment episodes (40%); the most frequently recorded complication was access dysfunction (26, 24.8%) followed by sepsis (15, 14.3%); citrate-related (3, 2.9%) and anaphylaxis (2, 1.9%) were relatively unusual. The probability of developing complications increased with the duration of PEX; women were at lower risk of developing complications compared to males (table 5). CDC stage did not appear to increase the risk of developing sepsis as a complication of PEX (P = 0.337).

Table 5. Factors affecting risk of PEX-related complications

	OR (95% CI)	P

Increasing age (years)	1.01 (0.95 – 1.09)	0.704
Female sex	0.12 (0.03 – 0.49)	0.004
Use of FFP as infusant	3.11 (0.71 – 13.67)	0.134
Number of daily PEX sessions	1.38 (1.18 – 1.63)	< 0.001
CDC stage	1.14 (0.38 – 3.45)	0.806
HIV viral load (copies/mL)	1 (0.99 – 1.00)	0.266

OR: odds ratio; CI, confidence interval

Median eGFR at remission in the 57 survivors of HIV-TTP was 96 mL/min/1.73m^2 (range, 53 – 152 mL/min/1.73m^2), a significant improvement from that recorded at presentation in these patients (median presenting eGFR 72 mL/min/1.73m^2, Wilcoxon matched pairs P < 0.001). Forty patients (70.2% of survivors) completed outpatient follow-up at least 2 months following discharge (median duration of outpatient follow-up 1489 days, equivalent to 49.6 months; range 60 – 3564 days). The median eGFR in these patients at most recent follow-up was 88.5 mL/min/1.73m^2 (interquartile range 74 – 111 mL/min/1.73m^2). eGFR at presentation was a significant determinant of long-term kidney function adjusted for duration of follow-up (table 6).

Commented [SH1]: Typo corrected

Table 6. Factors affecting renal function at long-term follow-up

	β (95% CI)	P
Increasing age (years)	-0.32 (-1.22 – 0.58)	0.476
HIV viral load (copies/mL)	0.00 (-0.00 – 0.00)	0.224
Haemoglobin (g/dL)	0.81 (-6.03 – 4.41)	0.772
LDH (IU/mL)	-0.01 (-0.01 – 0.00)	0.054
Platelet count (x10^9/mm^3)	-0.49(-1.51 – 0.53)	0.332
Number of PEX sessions to induce remission	-0.13 (-1.22 – 0.58)	0.772
eGFR (mL/min/1.73m^2)	0.38 (0.12 – 0.65)	0.006
Time to follow-up (days)	0.00 (-0.01 – 0.01)	0.892

Discussion

This large cohort confirms the association of HIV-associated TTP with advanced HIV infection; the disorder appears to show a female predilection. Neurological deficit is a common presenting feature of the disorder. HIV viral load appears to correlate with severity of kidney but not central nervous system target organ involvement. Inpatient mortality in HIV-TTP is high even with plasma exchange; death due to sepsis-related complications contribute a significant proportion of deaths. Renal function at presentation may predict mortality risk; choice of plasma infusant may additionally affect survival outcomes. Complications of PEX are not uncommon and risk of complication increases with duration of treatment. Significant residual renal impairment amongst HIV-TTP survivors is uncommon and correlates with severity of kidney injury at presentation.

Women and persons of Black African ethnicity are over-represented in TMA registry data. Low frequency of HLA-DRB1*04 in Black Africans has been associated with increased risk of TMA in this population.[19] Gender disparity in prevalence of autoimmune disease and the effect of oestrogen on endothelial function may underlie the female preponderance reported in TMA.[21],[22] In South Africa, the highest incidence of HIV infection is amongst young women of Black African ethnicity, due to gender and racial inequalities. [23] The propensity for young Black women to develop HIV-TTP in this and other local series [4],[5],[24] thus likely reflects selection for a population at increased risk of TMA by the demographics of the HIV pandemic in the local setting.

HIV-TTP is more commonly seen in patients with advanced HIV infection, seldom recurs in patients adherent to ARV therapy, and has shown decreasing incidence in countries with widespread ARV availability.[8] The duration of PEX needed to achieve remission in HIV-TTP has additionally been reported to correlate with viral load.[25] Such observations suggest a direct role for the virus in the pathophysiology of HIV-TTP. Presentation with HIV-TTP in this series was similarly associated with advanced HIV infection. However, excepting kidney dysfunction at presentation, no effect for severity of HIV infection on the presentation or outcomes of HIV-TTP were discernible in the present study.

Neurological deficits have previously been reported to be more frequent in HIV-TTP than in other forms of the disorder,[24] although it remains unclear whether this reflects an exacerbation of pre-existing cognitive disorders prevalent in PLWH or a predilection for central nervous system involvement by the thrombotic microangiopathic process resulting from neurotropism of the virus.[26],[27] The apparent correlation between viral load and severity of renal dysfunction in the present cohort may similarly reflect the ability of HIV to establish an infection compartment within the kidney [27] or the presence of underlying and undiagnosed HIV-related kidney disease.

Treatment guidelines recommend PEX as first-line therapy for HIV-TTP in conjunction with emergent ARV initiation [17] due to theoretical benefits including removal of autoantibody and UL-vWF, and facilitation of the infusion of a greater volume of replacement plasma. Actual evidence of the superiority of PEX over plasma infusion (PI) is limited, [11] Previous retrospective South African studies have reported favourable outcomes with PI therapy alone.[5],[24] The median duration of PEX therapy in the present series of 9 days is not markedly dissimilar from that reported by Masoet et al. for PI alone (10 days), with similar crude inpatient mortality rates being observed (45.7% and 43.9%, respectively).[5] We observed a higher contribution of sepsis-related deaths in our cohort (25.5% of mortalities) than that reported by Masoet et al. (11.1%) which may substantiate concerns of PEXaugmented immunocompromise in PLWH.[13]

Mortality in HIV-TTP in this and other cohorts therefore appears higher than that reported for other forms of the disorder.[6],[10] Better preserved renal function at presentation was associated with reduced risk of mortality, consistent with previous reports.[28] Since significant renal dysfunction was unusual in this series, uraemia itself is unlikely to explain this association. Instead, more severe renal dysfunction may serve as a marker for the involvement of other target organs; in particular, the risk of myocardial infarction due to coronary thrombotic microangiopathy.[29] Cryosupernatant plasma contains relatively low concentrations of UL-vWF and has previously been suggested to impart better remission rates than FFP;[30] this may partially account for the association between FFP use and increased risk of early inpatient mortality with the use of the latter in the present study.

There is a paucity of data on residual kidney impairment in most TTP series and little is known of the long-term renal sequelae in survivors of TTP-HIV. Numerically significant improvement in renal function was observed at attainment of remission in this cohort, which persisted at later outpatient follow-up. Longer duration of outpatient review is needed in order to better categorise the long-term effects of HIVTTP mediated AKI on risk of chronic kidney disease in survivors.

There are limitations to this study. The retrospective nature of this study is likely to have compromised accurate recording of clinical data such as the nature and severity of neurological deficit, which may in turn affect analysis of the contribution of such parameters to mortality outcomes. We also acknowledge the lack of ADAMTS13 data in this cohort occasioned by resource constraints. Although not required for the diagnosis of HIV-TTP, ADAMTS-13 activity may delineate mortality risk and would be a useful adjunct to analysis of this outcome. The retrospective nature of this study additionally requires reliance on contemporaneous assessment of the causes of mortality which may have compromised accurate description of this outcome. Disparate duration of outpatient follow-up, caused by patient default after discharge, additionally limits full evaluation of long-term renal outcomes. Finally, this study was performed in a single-centre which may raise concerns regarding the generalizability of our findings. However, we would suggest that this latter limitation conversely provides for homogeneity in the case definition and management of HIVTTP, thus limiting confounding factors.

Conclusion

HIV-associated thrombotic thrombocytopenic purpura occurs in the setting of advanced HIV infection. Poorer survival in HIV-TTP with plasma exchange compared to that reported for other forms of the disorder may partially be explained by exacerbation of HIV-related immunocompromise by this therapy as evidenced by significant sepsis-related complications. Comparison with previous studies of plasma infusion as sole therapy does not appear to show superiority of PEX in HIV-TTP. Choice of plasma infusant may affect outcomes. Further evaluation through

prospective randomized trials are needed to better evaluate the efficacy of PEX against PI and the optimal plasma infusant in HIV-TTP. Longer duration of follow-up in survivors is additionally required to better categorise renal sequelae.

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