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Human immunodeficiency virus associated thrombotic thrombocytopenic purpura (TTP) – favourable outcome with plasma exchange and prompt initiation of Highly Active Antiretroviral Therapy (HAART).

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2 Human immunodeficiency virus associated thrombotic thrombocytopenic
3 purpura (TTP) – favourable outcome with plasma exchange and prompt
4 initiation of Highly Active Antiretroviral Therapy (HAART).
5

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Abstract

Background: Thrombotic thrombocytopenic Purpura is an acute prothrombotic disorder. HIV is an identified precipitant. **Design and methods** Thirty episodes of HIV associated TTP in 24 patients from the South-East England Apheresis units, over past 10 years, are reviewed. **Results:** All patients were heterosexual Black Africans. First presentation of TTP revealed a new diagnosis of HIV in 8 patients. TTP relapse occurred on 6 occasions (in 4 patients) as a result of non-adherence to HAART. Prompt initiation/re-initiation of HAART in parallel with PEX +/- steroid led to prompt remission. Adjunct immunomodulatory agents (e.g.Rituximab) was required in 10% of cases. Once-daily HAART regimens are recommended, being compatible with PEX requirement, maximising drug exposure between PEX. High viral loads (>500,000copies/ml) require more PEX to remission. ADAMTS 13 activity was reduced (<5%) as detected by CBA and Anti-ADAMTS 13 IgG antibodies raised in 80%. Continued HAART-adherence ensured a durable TTP remission with associated viral control resulted in no evidence of relapse. **Conclusion:** PEX and HAART are associated with replenishment of ADAMTS 13 and viral suppression. More PEX is required in cases with higher viral loads. Continued HAART maintains remission. In a small proportion of cases, further immunomodulatory therapy may be required.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) results from a deficiency of von Willebrand factor-cleaving protease (vWF-cp) activity. ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13) is the enzyme identified as mediating this cleaving function (1). The loss of cleaving activity results in circulation of abnormal ultra large vWF multimers (ULvWF) provoking widespread microvascular thrombosis. Urgent plasma exchange (PEX) and adjunctive steroid therapy is the cornerstone of treatment for acquired TTP and has resulted in dramatic improvements in survival, from 10% in the pre-PEX era to 80-90% with current PEX-based regimens (2). Further improvements in clinical outcome of

1
2 idiopathic-TTP have been reported using anti-CD20 antibody (Rituximab) to reduce
3 relapse risk in antibody mediated idiopathic disease, accounting for the majority of
4 cases (3). Simultaneous in-vitro assay development has improved quantitation of
5 ADAMTS13 activity and detection of anti-ADAMTS13 antibodies (4). Human
6 immunodeficiency virus (HIV) associated TTP is a subgroup (5) defined as
7 secondary TTP, as there is a precipitant identified. In this paper we describe
8 patients with HIV-associated TTP registered in SE England TTP registry and
9 subsequently the UK registry (but within the SE England), over a 10 year period.
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14 15 **PATIENTS, MATERIALS AND METHODS** 16

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18 Twenty four HIV positive patients, eighteen of which were female, mean age 36
19 years (range 1 – 64) were identified from five South East England units offering
20 apheresis between 1998 and 2009. We have included eight patients previously
21 published (5). A total of 30 episodes of acute TTP were identified from this
22 population. Four patients had relapses (three experiencing a single relapse and the
23 remaining patient had three relapses). Clinical case notes were accessed when
24 necessary to complete data sets.
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30 Diagnosis of TTP was made using BCSH guidelines (6), on clinical grounds,
31 including thrombocytopenia and microangiopathic anaemia characterised by blood
32 film red cell fragmentation, reticulocytosis, normal coagulation screen, negative
33 direct antiglobulin test (DAT) and elevated lactate dehydrogenase (LDH), supported
34 by ADAMTS 13 assays. On diagnosis of TTP all patients received PEX and steroids
35 (either pulsed methylprednisolone or high dose oral steroids) as per local protocol.
36 Only four patients did not receive steroids on admission, typically if they were
37 already known to have HIV infection.
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41 Since 2004, ADAMTS13 activity has been undertaken by a modification of collagen
42 binding assay (CBA) (7), normal 66-126%, and before 2004, by multimer analysis (8)
43 (normal range 80 -120%. Inhibitory activity was determined by 1:1 mixing studies
44 with pooled normal plasma for 1 hour incubation at 37°C. Anti ADAMTS13 IgG
45 detected by a modified ELISA (3)
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RESULTS

Thirty episodes of HIV-related acute TTP were treated over the past 10 years. Twenty four cases, (seventeen women) represented a first episode of TTP, the remaining 6 episodes being TTP relapses. All patients were heterosexual Black Africans. In eight episodes, presentation with TTP resulted in a new diagnosis of HIV infection. The remaining twenty one episodes occurred in patients who were known to have HIV infection.

Presenting haematological parameters revealed universal thrombocytopenic (mean $20 \times 10^9/L$, range $5-107 \times 10^9/L$) a raised lactate dehydrogenase (LDH) (mean 2,285, range 464–8,000 IU/L) and variable levels of anaemia (mean presenting haemoglobin 6.8 g/dL (range 3 – 13.4g/dl). Nineteen cases presented with neurological symptoms ranging from headache and confusion to seizures and localising neurology **Table 1**. Ten patients had renal impairment at presentation, correcting to within the normal range with treatment. There was no deterioration in renal function on starting HAART. Four cases had cardiac symptoms/raised Troponin at presentation. Daily plasma exchange and concurrent initiation of HAART resulted in an average of 13.5 plasma exchange (PEX) (range 3 – 33), to remission, when calculated for the whole group.

In seven cases, despite previous anti-retroviral treatment, there was an increase in viral load associated with the initial presentation of TTP. One was receiving suboptimal single agent antiretroviral therapy and three episodes were thought to be adherent with HAART but had HIV resistance. One other case had demonstrable HIV-resistance mutations and rising viral load despite multiple HAART regimens. Rising viral load attributed to resistance was observed in a second case and no data was available for the third. Patients with HIV resistance mutations had not previously been reported as presenting with TTP at HIV diagnosis. HIV viral load was $>10,000$ copies/ml at TTP diagnosis in nineteen cases: three had viral loads $>500,000$ copies/ml; five between 100,000–500,000 copies/ml and nine between 10,000–100,000 copies/ml. Two cases presented with viral loads $<10,000$ copies/ml. Cases ($n=10$) with viral loads between 10,000-500,000 copies/ml required fewer PEX to remission (median 7.5 (range: 6-25). In those with viral loads $>500,000$ ($n=3$), the median PEX to remission was 27(12-30). The number of cases were too small to

1
2 formally review a statistical significance. Average CD4 count was $236 \times 10^6/l$ (n=24)
3 (range 70 – 540) on admission.
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5 Only one relapsed case and one de novo TTP required additional therapy;
6 Rituximab. In these cases, despite PEX, steroids and HAART with a reduction in
7 viral load, there was prolonged thrombocytopenia and ADAMTS 13 activity remained
8 <5%. One case received 2 infusions and the other 4 infusions ($375\text{mg}/\text{m}^2$), given
9 weekly. This resulted in prompt sustained remission, with no adverse effects
10 (specifically no infections). There was one death in this cohort, an atypical
11 presentation for HIV-associated TTP. The patient was already receiving HAART;
12 viral load was undetectable and remission induction and maintenance was difficult
13 despite PEX, steroids, Rituximab and continued HAART. The cause of death was
14 not determined. Although not formally tested, viral resistance and/or HAART non-
15 compliance was unlikely as the viral load was undetectable. A further case had
16 undetectable viral load, low ADAMTS 13 activity (<5%) and a raised Anti-ADAMTS
17 13 IgG (105%). They were already receiving HAART which was not altered on
18 admission and responded to PEX and high dose steroids.
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27 Patients who continued HAART associated with lowered, mainly undetectable viral
28 loads, have not relapsed. However, relapse was associated with stopping HAART
29 and re-presentation of TTP within 3 months. In twenty-four cases, pre-PEX
30 ADAMTS 13 activity data was available – in 16 patients was <5% by CBA and was
31 <50% in the remaining cases by the multimer assay. In eighteen cases, anti-
32 ADAMTS 13 IgG levels were available, median 24% (4-105%). Remission was
33 associated with normalisation of ADAMTS 13 activity; relapse resulted in a further
34 decreased ADAMTS 13 activity to <5%.
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41 DISCUSSION

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43 Survival of HIV-associated TTP in the pre-HAART era was rarely more than 2 years
44 despite improvements in acute TTP management with PEX and steroid treatment
45 (9). Our data confirms prompt, concurrent treatment with both PEX and HAART
46 results in a favourable outcome in most cases, with a low mortality of 4% of our
47 cohort. This is in contrast to acquired, idiopathic TTP, where mortality is 10-20%
48 (2;10). Indeed, when the patients are adherent with HAART therapy, the apparent
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2 relapse rate in this cohort is lower than historical relapse rates seen in idiopathic TTP
3 treated with PEX/steroid alone. TTP relapses were seen in patients with virological
4 rebound attributed primarily to non adherence with HIV therapy. One case was
5 repeatedly non-compliant and as a consequence has relapsed on multiple
6 occasions. One of these non-compliant relapses required adjunctive Rituximab to re-
7 induce a remission. Only one patient appeared refractory to PEX/steroids/HAART at
8 first presentation and consequently received Rituximab to achieve remission. Indeed,
9 Rituximab has been used successfully in HIV-TTP (11). Rituximab therapy has
10 impacted significantly on refractory and relapsing TTP in non-HIV TTP (3). However,
11 in the context of HIV associated TTP, we believe immunomodulatory therapy such
12 as Rituximab, should only be considered in the unlikely scenario of primary
13 resistance to PEX/steroid/HAART and after HAART non-adherence or HIV
14 resistance have been excluded. There appears to be no association with the Anti-
15 ADAMTS 13 IgG titre and the clinical severity of HIV-associated TTP, which is in
16 contrast to idiopathic TTP, where antibody associated TTP has a more aggressive
17 clinical presentation (10). Therefore, the immune component in the pathophysiology
18 of this subgroup appears generally less relevant than the direct effect of the
19 retrovirus. Why these specific patients develop TTP rather than other HIV associated
20 complications, either as a presenting event or with resistant disease remains
21 unanswered.

22
23 ADAMTS 13 assays are useful in helping to confirm a diagnosis of TTP. CBA and
24 more recently FRETs assay are more sensitive and specific, compared to multimeric
25 analysis. All patients achieving remission had a normal ADAMTS 13 activity that was
26 maintained while patients continued HAART.

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28 Fifteen cases in this cohort were known to be HIV positive and already on HAART,
29 and all but one had a change made to their HAART regimen upon presenting with
30 TTP. Indeed optimisation of HIV therapy with new drugs was required to achieve
31 virological suppression and utilising combination therapy advance remission of TTP.
32 Of interest, those with a viral load between 10,000 and <500,000 copies/ml at
33 presentation, regardless of a new presentation or previously diagnosed HIV, required
34 fewer PEX to remission than those with higher viral loads (>500,000 copies/ml).
35 Cases treated promptly with PEX/steroid/HAART therapy achieved a robust
36 remission if they continued HAART and achieved suppression of the viral load.
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2 A single patient in this cohort achieved prompt TTP resolution with steroid and
3 plasma infusion alone, prior to transfer for plasma exchange. Plasma infusion has
4 been reported as being sufficient to achieve remission either in the absence of
5 available PEX facilities (12) or in the context of patient non-compliance with PEX
6 (11). However, administration of such large volumes of plasma causes considerable
7 clinical problems. Plasma infusion should be used with steroid in the event of delay
8 transferring to a PEX facility and plasma exchange should remain the gold standard
9 therapy for HIV associated TTP when logistically possible.
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15 The unwell, HIV-positive patient presenting with thrombocytopenia demands
16 consideration of a broad differential diagnosis list (13;14). However, TTP remains
17 one of the most important clinical diagnoses requiring immediate treatment rather
18 than deferred treatment pending confirmatory testing or exclusion of other
19 diagnoses. The cohort we have presented had no evidence of other HIV associated
20 TMA, such as HUS or opportunistic infection. We did not see, as recently reported,
21 increased mortality rates in HIV-TTP (15). ADAMTS 13 activity in our cohort could
22 not be used as a predictor of outcome and only one of our cases had other AIDS
23 defining complications. Patients with advanced HIV disease may have
24 thrombocytopenia and red cell fragmentation alone, rather than displaying other
25 thrombotic phenomena, in keeping with HIV thrombotic microangiopathy, rather than
26 HIV associated TTP. (16).
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35 The cohort consists of HIV cases presenting over a period of a decade, in which time
36 there have been significant changes in anti-retroviral preparations and combinations.
37 Although no conclusions can be drawn as to the optimal HIV treatment regimen
38 required to expedite remission, safe combinations enabling once daily administration
39 are ideal. We believe that HIV treatment should be administered immediately with
40 the aim to suppress circulating HIV virus as quickly as possible. As an HIV
41 resistance result may not be available at the time of starting treatment, a once daily
42 boosted protease inhibitor (which has a high genetic barrier to resistance) should be
43 included in the regimen. In addition, HIV therapy including raltegravir has been
44 shown to result in a more rapid decline in HIV viral load that standard triple
45 combination therapy. HAART should be administered immediately after PEX,
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2 maximising drug exposure and minimising chance of drug removal with subsequent
3 PEX.
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6 As an autoimmune phenomenon, women are more commonly affected by idiopathic
7 TTP than men (10). This gender skew (70% female) is also evident in this HIV-
8 associated TTP cohort, relative to 58% of new HIV diagnoses being women.
9 However, the striking skew to patients of African origin in the HIV-TTP setting
10 (100%), compared to only 34.7% of new HIV diagnoses in the UK being of African
11 origin, is more difficult to explain, but may suggest a possible underlying genetic
12 predisposition.⁽¹⁷⁾
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18 In conclusion, thrombocytopenia in HIV is relatively common and potential causes
19 and underlying mechanisms may vary significantly, However, HIV-associated TTP
20 remains an important diagnosis, particularly in heterosexual, mainly female Black
21 African patients. We emphasise the importance of prompt identification of the HIV-
22 positive status and urgent initiation of HAART in parallel to PEX. Those with the
23 highest viral loads at presentation (>500,000 copies/ml) required more PEX to
24 remission than those with viral loads <500,000 copies/ml. If TTP is diagnosed in an
25 HIV positive patient already on HAART, adherence and/or resistance studies should
26 be considered. Rarely, further immunomodulatory therapy such as Rituximab may be
27 needed. A patient's adherence with HAART ensuring continued viral suppression
28 prevents further TTP relapse.
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Patient	age at presentation (years)	gender	Ethnicity	New diagnosis HIV	Platelets on admission ($\times 10^9/L$)	LDH on admission (IU)(NR<480IU)	Hb on admission (g/d L)	Viral load on admission (Copies/ml)	CD4	Symptoms	No.of PEX	Commenced HAART
1	30	F	Black African	Y	8	3078	9.4	854,000	70	n,f	12	n
2	27	M	Black African	Y	10	3317	8.9	n/a	n/a	f,r	20	e,c
3a	23	M	Black African	N	7	2390	6.7	67,800	170	n	16	l,lm,a
4	45	F	Black African	Y	15	1967	8.1	19,500	400	n,b	16	dd,tc,k
5a	44	F	Black African	N	16	914	4.6	47,100	170	n,r	7	l,lm,d
6	35	F	Black African	n/a	46	n/a	6.3	n/a	n/a	n	13	k,az
7	1	M	Black African	N	20	>8000	6.5	>500,000	260	n	30	z,lm,k
8	40	F	Black African	Y	11	5009	6.0	51,900	130	n,a,r,c	8	l,tc,dd
9a	37	F	Black African	N	14	2196	8.5	n/a	190	n,f	5	l
10	38	F	Black African	N	9	483	7.8	48,000	490	n	6	*t,d4,tc,k,at
11	35	F	Black African	Y	12	975	5.4	n/a	320	n,f	11	l,lm,d
12	32	F	Black African	N	22	3500	6.6	467,000	50	n,r	5	z,lm,nv
13	37	F	Black African	N	53	1234	6.8	n/a	209	n,f,c	9	*s,lm,nl
14	41	F	Black African	Y	45	1673	5.5	12,617	250	N/A	6	s,lm,nl
15a	39	F	Black African	N	9	2124	5.3	>500,000	200	n	27	tr,l
16	33	F	african	N	8	3139	5.1	230,000	420	tired	25 + Ritux	da,r,tr

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9 **Table 1a: HIV-TTP Presenting features and treatment of first presentation**

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f:fever	#existing combination	d:didanosine
r:renal	* change of existing combination	az: azt
a:abdo	n: commenced but details unavailable	z: zidivudine
n:neuro	e: efavirenz	t:tenofovir
c:cardiac	c: combivir	d4: d4t
b:bleeding	l: lopinavir	at: atazanavir
	lm: lamivudine	nv: nevirapine
	a: abacavir	s: stavudine
	dd:ddi	nl: nelfinavir
	tc: 3TC	tr:truvada
	k: kaletra	da:darunavir
		r: ritonavir
		ki:kivexa

Patient	Age (years)	gender	ethnicity	Platelets on admission (x10 ⁹ /L)	LDH on admission (NR<480 IU)	Hb on admission (g/d L)	viral load on admission (copies/ml)	CD4	PEX to remission
3b	23	M	Black African	8	1967	7.2	19,500	230	6
3c	27	M	Black African	15	464	9.8	90,000	180	7.5
3d	28	M	Black African	5	2435	11.5	600	200	33
5b	45	F	Black African	26	1068	7.2	n/d	60	3
9b	39	F	Black African	7	Haemolysed	3.0	490,000	90	6
15b	40	F	Black African	107	467	13.4	n/d	n/d	8

Table 1b: Relapsed TTP-HIV cases. b/c/d refer to episode. The number refers to initial episode in table 1a.