# Response and remission after first line corticosteroid therapy in primary ITP

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**Declaration**

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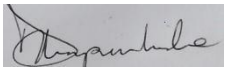
Signature: 

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**Format**

This is a publication-ready manuscript formatted according to the guidelines of The South African Medical Journal (SAMJ).

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**List of Abbreviations**

| | |
|---|---|
| ANA | Antinuclear antibody |
| ASH | American Society of Haematology |
| BME | Bone marrow examination |
| CR | Complete response |
| GSH | Groote Schuur Hospital |
| HIV | Human Immunodeficiency Virus |
| IDA | Iron deficiency anaemia |
| IDT | Iron deficiency thrombocytopenia |
| ITP | Immune thrombocytopenia |
| NR | No response |
| PR | Partial response |
| SLE | Systemic lupus erythematosus |
| TTR | Time to respond |

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**Publication-ready Manuscript**

**Title**

Response and remission after first line corticosteroid therapy in primary ITP

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**Abstract**

**Background:** Primary immune thrombocytopenia (ITP) is an acquired autoimmune disease characterized by an isolated thrombocytopenia of <100 x $10^9$/L in the absence of identifiable secondary causes. Treatment is indicated when the platelet count is <20-30 x $10^9$/L, but may be commenced at higher platelet counts when the risk of bleeding is high. Corticosteroids are

the backbone of initial treatment of ITP. There is a paucity of data in South Africa on the outcomes of newly diagnosed ITP patients treated with corticosteroids.

**Objectives:** To describe the response, remission and clinical outcomes of newly diagnosed primary ITP patients on first-line corticosteroids.

**Methods:** This was a retrospective cohort study of 68 patients with a new diagnosis of ITP, seen at the Clinical Haematology Unit at Groote Schuur Hospital, over a 5-year period (20162020). Demographic and clinical data were obtained from paper and electronic record systems. All participants with secondary causes were excluded. The initial platelet responses to corticosteroids and the final outcomes at last follow up were determined. Initial platelet responses were classified into no response (NR), partial response (PR) and complete response (CR) in accordance with consensus definitions. Remission was defined as maintenance of a CR after being off corticosteroids for at least 6 months. Variables were described by frequencies and percentages or medians and interquartile ranges, as appropriate. Categorical variables were described by frequencies and percentages while numerical variables were described by medians and interquartile ranges as data were non-parametric.

**Results:** The majority of patients were females (88.2%) and the median age at diagnosis was 36 years (IQR 23.0-55.5). The female to male ratio was 7.5:1. Most patients responded to corticosteroids (92.4%) with 74.2% achieving a CR and 18.2% achieving a PR. Only 5 patients failed to respond (7.6%). The median time to achieve CR was 15 (IQR: 8-25) days and the median time to achieve PR was 10.5 days (IQR 822). Half of the patients went into remission. Following remission, two patients (6.1%) subsequently relapsed at day 344 and day 777, respectively. Hypertension and/or diabetes were newly diagnosed in 10.6 % of patients.

**Conclusion:** Corticosteroids are effective first line therapy for ITP but are not remission inducing in all patients. For those patients progressing to chronic ITP, there is a need to investigate cost effective treatment. Some patients are at high risk of developing new hypertension and diabetes mellitus on corticosteroids and should be monitored.

## Introduction

Primary immune thrombocytopenia (ITP) is an autoimmune disease defined by an isolated thrombocytopenia of < 100 × $10^9$/L in the absence of distinguishable secondary causes (1, 2). The worldwide incidence varies from 2-4 cases per 100,000 person-years, affecting more females and increasing with age (3-5). The depleted platelet pool is a result of several incompletely understood pathophysiological processes, namely platelet autoantibodies, depressed megakaryocytopoiesis and T-cell mediated cytotoxicity (6, 7). Following new diagnosis, the clinical picture is diverse but in the majority the disease runs a mild course with bleeding episodes mostly occurring with platelet counts of less than 10-20 × $10^9$/L (8). In newly diagnosed adults with primary ITP, the indication of treatment is a platelet count < 20-30 × $10^9$/L, but treatment may be started at higher platelet counts when the bleeding risk is high, for example, in patients prone to falls or accidental injury (9). In the Human Immunodeficiency Virus (HIV) endemic region of Southern Africa, the main cause of secondary ITP is HIV and the prevalence of thrombocytopenia amongst people living with untreated HIV is 30-40% (10). Due to a perceived wider range of differential diagnoses in this environment, bone marrow examination (BME) for isolated thrombocytopenia is not uncommon and was performed in 21% and 14.3% of HIV patients in two previous local studies, respectively (11, 12). Indications for BME in HIV uninfected patients are age > 60 years, the presence of clinically concerning systemic symptoms and signs suggesting primary or secondary bone marrow pathology, and in preparation for splenectomy (1).

First line treatment of ITP encompasses corticosteroids which have been in use for ITP since the 1950s (13). Intravenous immunoglobulins and anti-D immunoglobulins are useful as rescue therapy to achieve rapid haemostasis (9). Corticosteroids have broad anti-inflammatory and immunosuppressive effects and modulate endothelial function, ultimately reducing bleeding risk (14). The gold standard of treatment is a 4-day regimen of 40 mg dexamethasone intravenously daily, repeated monthly; or 0.5-2 mg/kg of prednisone orally which is gradually weaned over four to six weeks and then withdrawn (9). Initial response is classified into no response (NR), partial response (PR) and complete response (CR) and measured within the first 10 days for those receiving dexamethasone and the first 28 days for those receiving prednisone (2). This initial response rate to corticosteroids ranges from 60-80%, but only 3055% of patients remain in remission (15-17). It is the responsibility of physicians to ensure that patients are sufficiently monitored for conceivable corticosteroid side effects, the most immediate of which are hypertension and hyperglycaemia (9). Other notable side effects of corticosteroids are weight gain, osteoporosis, peptic ulcers, impaired wound healing, psychosis and increased risk of infections (18).

There is limited research in sub-Saharan Africa on the diagnosis and treatment of primary ITP. Two South African centres previously favourably reported on the role of splenectomy in second-line treatment of ITP patients (19, 20). Two other local studies reported that IVIG had no advantages over oral corticosteroids as primary therapy for ITP (21, 22). An unpublished dissertation retrospectively analysing 243 patients over a 25-year period at another South African hospital showed that 65% of patients with primary and secondary ITP achieved CR after corticosteroids (23). What is not known in our local cohort is the response rate and remission rates of patients with primary ITP on first-line corticosteroid therapy. To this aim we

reviewed all patients who attended our ITP clinic in the Clinical Haematology Unit at Groote Schuur Hospital (GSH), during the period of 2016 to 2020, for clinical characteristics and treatment outcomes.

## Methods

### *Study design and patient selection*

This retrospective cohort study included patients with newly diagnosed ITP managed in the Clinical Haematology Unit at GSH, a tertiary and quaternary public health care facility in Cape Town, South Africa, from January 2016 to December 2020. Approval for the study was obtained from the Human Research Ethics Committee at the University of Cape Town (HREC 197/2022). Patients treated at the Clinical Haematology Unit at GSH are included in the clinic's electronic patient registry. A waiver of written consent for retrospective data collection is in place for patients included prior to 2018 and informed consent is obtained for patients included from 2018 onwards.

### *Diagnostic criteria*

ITP is defined as an isolated thrombocytopenia (platelet count $<100 \times 10^9$/L) in the absence of other conditions or causes associated with thrombocytopenia (2). A diagnosis of primary ITP is made after secondary causes of ITP are excluded (2). The diagnosis of ITP was confirmed by careful review of the clinical history (including drug list and known medical conditions) and clinical and laboratory examination to differentiate between primary ITP and secondary ITP. The full blood count, differential count, peripheral blood smear and the results of other laboratory tests in particular HIV, hepatitis B and C virus, and ANA (antinuclear antibodies) were recorded and reviewed for significance (i.e., reported in the literature to be associated with ITP). Patients with proven HIV, Hepatitis B and C, and systemic lupus erythematosus (SLE) were categorized as secondary ITP. ANA positivity alone, was not seen as an exclusionary criterion in the absence of characteristic clinical manifestations suggestive of SLE (2, 24, 25). Other causes of secondary ITP were considered.

### *Demographic and clinical data*

Patient demographic and clinical data were obtained from patient files and electronic record systems. Demographic data collected included age and gender. Clinical data collected at presentation included presenting symptoms, diagnosis setting, blood results (platelet count, haemoglobin level and ferritin level), and the presence or absence of iron deficiency anaemia (IDA), diabetes and hypertension. Presenting symptoms were categorized as critical bleeding, other bleeding, only bruising, asymptomatic and unclear. Critical bleeding was defined as haemorrhage into a critical anatomical site including intracranial, intraocular, intraspinal, pericardial, retroperitoneal, or intramuscular with compartment syndrome; or continuous haemorrhage that resulted in haemodynamic or respiratory compromise (26). IDA was defined as per the World Health Organisation (WHO) definition for iron deficiency (a ferritin <30 ng/mL) and anaemia (low haemoglobin of <12 g/dL in non-pregnant females, <11 g/dL for pregnant females and <13 g/dL in males) (27). Hypertension and diabetes were diagnosed by clinicians in accordance with local guidelines and was recorded at presentation with ITP. BME

at diagnosis was done at the clinicians' discretion. The institutional policy mandated BME in patients >60 years of age (1).

*Patient outcomes on first-line therapy*

For first-line corticosteroid therapy in the primary ITP cohort, outcome data was collected. This data included response to first-line corticosteroids, time to response to first-line corticosteroids, development of a new diagnosis of hypertension and diabetes, achievement of remission, relapse, and death. For patients who demised on first-line corticosteroids, the cause of death and timing from diagnosis were considered.

Types of corticosteroids administered were dexamethasone, prednisone or a combination of the two. Responses to corticosteroids were measured as per the International Working Group, where CR is defined as a platelet count of a minimum of $100 \times 10^9$/L; PR as a platelet count between 30 and $100 \times 10^9$/L and no less than doubling of the baseline platelet count; and NR as any platelet count below $30 \times 10^9$/L or lower than doubling of the baseline platelet count [2]. According to the American Society of Haematology (ASH) guidelines of 2019, remission is defined as a platelet count of $>100 \times 10^9$/L lasting at least 12 months (9). However, for the purposes of this study in the setting of first-line corticosteroid therapy, this criterion included the patient being off corticosteroid therapy for at least 6 months. Relapse was defined as a loss of CR or PR (2). For non-responders or those with a loss of response, a BME was done at the discretion of the treating clinician.

*Statistical Analysis*

Data was analysed using STATA V14 (Stata Corporation, College Station, Texas, USA). Categorical variables were described by frequencies and percentages. Numerical variables were described by medians and interquartile ranges as data were non-parametric.

**Results**

A total of 101 patients were referred to our facility with newly diagnosed ITP from 2016 to 2020 (Figure 1). Thirty-three patients were found to have a secondary cause of ITP and were excluded. The final cohort comprised 68 patients meeting the criteria for primary ITP. Baseline characteristics of the patients are presented in Table 1. The median age of the cohort was 36 years (IQR 23.0-55.5) and the majority of patients were female (88.2%). The female: male ratio was 7,5:1. The proportion of patients over 60 years of age was 17.6%. The median platelet count at presentation was $5 \times 10^9$/L (IQR 1.0-16.5) and 3 patients had critical bleeding. Two patients survived intracerebral haemorrhage without residual neurology and one had fatal gastrointestinal bleeding (an 84-yearold hypertensive woman with a platelet count of $0 \times 10^9$/L at diagnosis who died 6 days after diagnosis following appropriate dexamethasone therapy). Of the 68 patients, 53 (77.9%) were diagnosed as in inpatients with a median hospital admission duration of 7 days (IQR 4-10).

A significant proportion of patients had comorbidities, namely hypertension in 41.2% and diabetes in 14.7%. Five patients were ANA positive but did not meet the other criteria for SLE. These ANA positive patients did not progress to SLE during this retrospective study's time

frame. Out of the ANA positive group, two patients went into remission after corticosteroids and the rest had persistent disease. Approximately one quarter (23.5%) of patients had IDA at the time of ITP diagnosis. A total of 22 patients had a BME performed, 8 of whom were >60 years old. The median age at time of BME was 44 years of age. All BMEs were diagnostic except for 5 (22.7%) which were done when patients had a poor response to therapy (Table 1). All BMEs supported a diagnosis of primary ITP.

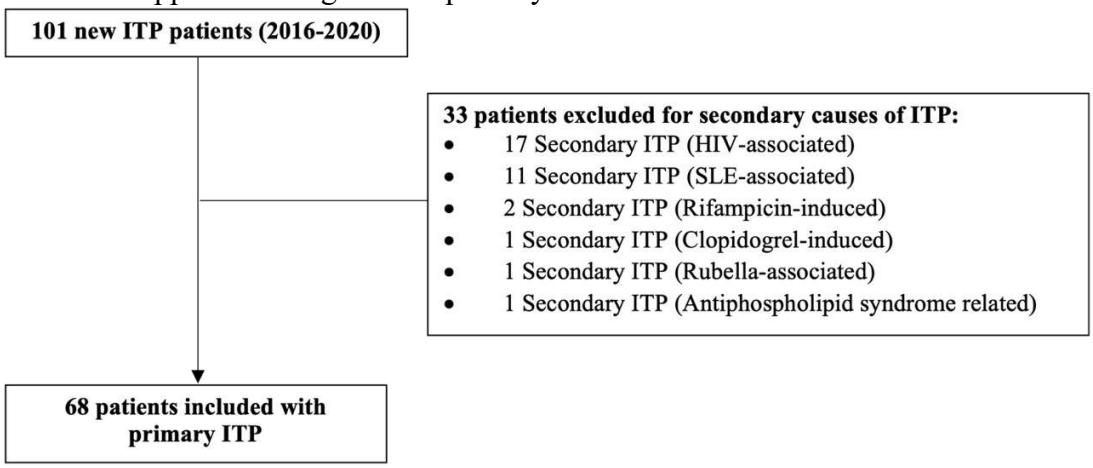


**Figure 1:** Flow chart of patients included in this study

**Table 1:** Baseline characteristics of 68 patients with primary ITP diagnosed from 2016 until 2020 and treated with first-line corticosteroid therapy in the Clinical Haematology Unit.

| **Characteristic** | **Number of patients n (%) or median (IQR)** |
|---|---|
| **Age at diagnosis** (years) | 36 (23.0-55.5) |
| **Gender** | |
| Male | 8 (11.8) |
| Female* | 60 (88.2) |
| **Female to male ratio** | 7.5:1 |
| **Presenting Symptoms** | |
| Critical bleeding | 3 (4.4) |
| Other bleeding | 45 (66.2) |
| Bruising only | 6 (8.8) |
| Asymptomatic | 11 (16.2) |
| Unclear | 3 (4.4) |
| **Blood results at diagnosis** | |
| Platelet count ($\times 10^9$/L) | 5.0 (1.0-16.5) |
| Haemoglobin (g/dL) | 11.1 (8.5-13.1) |
| Ferritin (n=42) | 26.0 (11.0-93.0) |

| | |
|---|---|
| **Comorbidities at diagnosis** | |
| Diabetes Mellitus | 10 (14.7) |
| Hypertension | 28 (41.2) |
| **Iron deficiency anaemia** | 16 (23.5) |
| **Setting of diagnosis** | |
| In patient | 53 (77.9) |
| Outpatient | 15 (22.1) |
| **Duration of hospital admission in days** | 7 (4-10) |
| **Bone marrow examination** | 22 (32.4) |

IQC, interquartile range

*5 patients were pregnant at the time of diagnosis.

Treatment responses and clinical outcomes on corticosteroids and response times are shown in in Table 2. Two patients were excluded from the treatment response analysis. The first exclusion was the elderly woman described above who died of gastrointestinal haemorrhage and the second exclusion was a 44-year-old man with a platelet count of 45 $\times 10^9$/L at diagnosis, who was managed with clinical observation only. The initial response rate was 92.4% (CR or PR) with 74.2% achieving a CR and 18.2% achieving a PR. Only 5 patients (7.6%) failed to respond to corticosteroids. The median time to response (TTR) for those achieving CR was 15 (IQR: 825) days and for those achieving PR it was 10.5 days (IQR 8-22). Half of the patients went into remission. Two of these patients (6,1%) relapsed – at 344 days and 777 days. One was a previously well 22-year-old female who was ANA positive and the other a 44-year-old female with IDA at diagnosis.

Table 3 shows patients known with, and diagnosed with diabetes mellitus and hypertension on corticosteroid therapy according to remission status. Of the patients who did not achieve remission, 51.5% had hypertension at diagnosis while 21.2% had diabetes mellitus at diagnosis. After corticosteroid therapy, 5 patients developed new onset diabetes mellitus, 1 patient developed hypertension and 1 patient developed both diabetes mellitus and hypertension. There were no noteworthy differences between those who developed comorbidities and remission status.

**Table 2:** Treatment response, median time to platelet response and clinical outcomes of first line corticosteroids in 66 patients*

| **Platelet response** | **n (%)** | **Time to response (days)** | **Remission achieved** |
|---|---|---|---|
| **No response** | 5 (7.6) | - | 0 |
| **Partial response** | 12 (18.2) | 10.5 (8-22) | 0 |
| **Complete response** | 49 (74.2) | 15 (8-25) | 33 (50) |

*2 patients excluded from treatment response: 1 patient demised within a week of diagnosis; 1 patient was only observed.

**Table 3:** Comorbidities at diagnosis and co-morbidities developed during treatment by remission status, in patients receiving first line corticosteroids treatment.

| | **Remission achieved (n=33)** | **Remission not achieved (n=33)** |
|---|---|---|
| **Comorbidities at diagnosis** | | |
| Diabetes Mellitus | 2 (6.1) | 7 (21.2) |
| Hypertension | 9 (27.3) | 17 (51.5) |
| **Comorbidities developed during treatment** | | |
| New onset diabetes mellitus | 2 (6.1) | 3 (9.1) |
| New onset hypertension | - | 1 (3.0) |
| New onset diabetes mellitus and hypertension | 1 (3.0) | - |

Values reported as number (%)

## Discussion

There is limited published data on the epidemiology and treatment responses to corticosteroids among patients with primary ITP in sub-Saharan Africa. Over this 5-year period, the median age of patients newly diagnosed with ITP was 36 years with a strong female predominance. This is not in keeping with European data showing an older median age group of 55 - 60 years and a slight female preponderance (28, 29). Our findings are more comparable to those reported in an unpublished dissertation on ITP at another quaternary hospital in South Africa that showed a median age of 32 years with just over 80% being females (23). The younger age group in Africa can be explained by the generally younger population in developing countries. Our median platelet count of $5 \times 10^9$/L is slightly lower than $10 \times 10^9$/L reported in the local South African study above (23). Published data in Europe show slightly higher median platelet counts of 12-20 x $10^9$/L (30, 31). The lower platelet counts in Africa are likely a reflection of delayed presentation due to poor patient accessibility to health care. The median TTR to corticosteroids was shorter in the partial responders (10.5 days) compared to the complete responders (15 days). This is within the expected 4 - 28 days to reach peak response (2). Our study's TTR is however longer than the 3-6 days median TTR shown in an Asian study (32). Following corticosteroid therapy, the response rate was 92.4% and remission rate was 50%. This is comparable to other studies with response rates to corticosteroids of 60-80% and remission rates of 30-55% (15-17).

BMEs were performed in 22 participants, of whom 8 were > 60 years of age. According to the ASH guidelines at that time, BMEs were performed to exclude haematological malignancies that may mimic ITP, in particular myelodysplastic syndrome (MDS) (33). We performed diagnostic bone marrows on 25.8% of the cohort which is lower than the 37.8% of diagnostic BMEs reported in a Scandinavian review done from 2009-2017 (34). The higher percentage in Europe is multifactorial and possibly due to a combination of the older population, guidelines recommending diagnostic BMEs for those > 60 years old and improved patient access to health care (1).

The percentage of patients (26%) diagnosed with IDA is higher than the published 10% prevalence in the 'healthy' South African adult population (35, 36). This is likely explained by delayed presentation of a population already at risk of IDA. IDA is often associated with reversible extremes of platelet count(37). The typical picture of IDA is associated with a reactive thrombocytosis; however, IDA is rarely associated with a thrombocytopenia – a term called iron deficiency thrombocytopenia (IDT) (38, 39). Platelet counts in both conditions respond rapidly to the correction of IDA. Platelet counts in ITP tend to be much lower (median $<10 \times 10^9$/L) than those in IDT (median $>30 \times 10^9$/L) (38). In our ITP patients with IDA, there was only one patient with a platelet count $>30 \times 10^9$/L; supporting the likelihood of ITP over IDT.

Prior to corticosteroid use, more than 50% of the patients had hypertension and diabetes mellitus. After corticosteroid exposure, another 10.6% of participants developed new onset diabetes mellitus and hypertension. Meta-analyses have demonstrated that the occurrence of diabetes is 1-
50% in previously normoglycemic people following a month or more of exposure to corticosteroids (40, 41). The prevalence of corticosteroid-induced hypertension is unclear but the risk increases with daily doses equivalent to 7.5mg of prednisone or more (41). ITP treatment consists of much higher doses of prednisone given for at least a month and there is a need to monitor patients for these side effects.

This study has some limitations including the retrospective design of the study. It was impossible to measure the treatment outcomes of dexamethasone in comparison to prednisone. This is because most patients ended up receiving both regimens. This was likely done as a safety precaution in case of missed appointments. The treatment regimens prescribed did not always follow treatment and some patients were inappropriately kept on high doses of prednisone beyond the recommended times. This created problems in classification of these patients into remission status.

## Conclusions

There is a paucity of data to date on primary ITP in sub-Saharan Africa. In this cohort, we find that primary ITP is a disease of predominantly young women. Corticosteroids are justified frontline agents for ITP due to their availability and their impressive initial response rate in our setting. However, they are not remission inducing in all patients, which is in accordance with the results obtained in Europe and America (15-17). The high doses of corticosteroids used to treat ITP further expose patients to the risk of newly diagnosed hypertension and/or diabetes mellitus. In our setting it is unclear whether dexamethasone is more efficient than prednisone as shown in other studies (17, 32). This study had several limitations due to its retrospective nature. A prospective study evaluating the efficacy of oral corticosteroids in comparison to dexamethasone would be useful.

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## Conflict of Interest

None

## Author Contributions

Prof Estelle Verburgh conceptualised the study. Dr Danai Mapimhidze collected data and wrote the article. Jenna Oosthuizen and Karryn Brown assisted with data management, performed the statistical analysis and edited the manuscript. Prof Estelle Verburgh and Dr Jenique Bailly reviewed and corrected the final manuscript.

## Funding Sources

None

## References

1. Provan D., et al., International consensus report on the investigation and management of primary immune thrombocytopenia. Blood. 2010;115(2):168-86.
2. Rodeghiero F., et al., Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113(11):2386-93.
3. Kurata Y., et al., Epidemiology of primary immune thrombocytopenia in children and adults in Japan: a population-based study and literature review. International Journal of Hematology. 2011;93(3):329-35.
4. Feudjo-Tepie MA., et al., The Incidence of Idiopathic Thrombocytopenic Purpura (ITP) among Adults in the United Kingdom's General Practice Research Database (GPRD), 1992–2005. Blood. 2007;110(11):3209-.
5. Frederiksen H., C.F. Christiansen, and M. Nørgaard, et al., Risk and prognosis of adult primary immune thrombocytopenia. Expert Review of Hematology. 2012;5(2):219-28. 6.
Zhou B., et al., Multi-dysfunctional pathophysiology in ITP. Critical Reviews in Oncology/Hematology. 2005;54(2):107-16.
7. Najean Y., et al., The Platelet Destruction Site in Thrombocytopenic Purpuras. British Journal of Haematology. 1967;13(3):409-26.
8. Piel-Julian M., et al., Risk Factors for Bleeding, Including Platelet Count Threshold, in Newly Diagnosed ITP Patients. Blood. 2017;130(Supplement 1):1041-.
9. Neunert C., et al., American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829-66.
10. Woldeamanuel GG and Wondimu DH. Prevalence of thrombocytopenia before and after initiation of HAART among HIV infected patients at black lion specialized hospital, Addis Ababa, Ethiopia: a cross sectional study. BMC Hematol. 2018;18:9.
11. Opie J. Haematological complications of HIV infection. S Afr Med J. 2012;102(6):465-8.

12. Abdullah I., et al., Indications and diagnostic value of bone marrow examination in HIV-positive individuals: A 3-year review at Tygerberg Hospital. S Afr J Infect Dis. 2021;36(1):273.
13. Stasi R and Newland AC. ITP: a historical perspective. British Journal of Haematology. 2011;153(4):437-50.
14. Salama A., Current & Emerging Treatments for Immune Thrombocytopenia. London: Future Medicine Ltd; 2013:60-4.
15. Vianelli N, Valdrè L., et al., Long-term follow-up of idiopathic thrombocytopenic purpura in 310 patients. Haematologica. 2001;86(5):504-9.
16. Schiavotto C and Rodeghiero F. Twenty years experience with treatment of idiopathic thrombocytopenic purpura in a single department: results in 490 cases. Haematologica. 1993;78(6 Suppl 2):22-8.
17. Mithoowani S., et al., High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and metaanalysis. The Lancet Haematology. 2016;3 10:e489-e96.
18. Stanbury RM and Graham EM. Systemic corticosteroid therapy--side effects and their management. Br J Ophthalmol. 1998;82(6):704-8.
19. Antel K.R., E. Panieri, and N. Novitzky., Role of splenectomy for immune thrombocytopenic purpura (ITP) in the era of new second-line therapies and in the setting of a high prevalence of HIV-associated ITP. South African Medical Journal. 2015;105: 408+.
20. Abdulraheem T.R., Impact of splenectomy on the management of Immune Thrombocytopenia in adults. In: Witwatersrand University, editor. 2018.
21. Jacobs P., et al., Intravenous gammaglobulin has no advantages over oral corticosteroids as primary therapy for adults with immune thrombocytopenia: A prospective randomized clinical trial. The American Journal of Medicine. 1994;97(1):55-9.
22. Jacobs P and Wood L. The comparison of gammaglobulin to steroids in treating adult immune thrombocytopenia. An interim analysis. Blut. 1989;59(1):92-5.
23. Variava F. Immune thrombocytopenia at Chris Hani Baragwanath Hospital. 2014. 24. Kurata Y., et al., [Clinical significance of antinuclear antibody in patients with idiopathic thrombocytopenic purpura]. Rinsho Ketsueki. 1992;33(9):1178-82.
25. Aringer M, Johnson SR. Systemic Lupus Erythematosus Classification and Diagnosis. Rheum Dis Clin North Am. 2021;47(3):501-11.
26. Sirotich E., et al. Definition of a critical bleed in patients with immune thrombocytopenia: Communication from the ISTH SSC Subcommittee on Platelet Immunology. Journal of Thrombosis and Haemostasis. 2021;19(8):2082-8.
27. Daru J. UK guidelines on the management of iron deficiency in pregnancy. British Journal of Haematology. 2019.
28. Frederiksen H and Schmidt K. The Incidence of Idiopathic Thrombocytopenic Purpura in Adults Increases With Age. Blood. 1999;94(3):909-13.
29. Neylon AJ., et al., Clinically significant newly presenting autoimmune thrombocytopenic purpura in adults: a prospective study of a population-based cohort of 245 patients. British Journal of Haematology. 2003;122(6):966-74.

30. Steurer M., et al., A large observational study of patients with primary immune thrombocytopenia receiving romiplostim in European clinical practice. Eur J Haematol. 2017;98(2):112-20.
31. Palau J., et al., Characteristics and management of primary and other immune thrombocytopenias: Spanish registry study. Hematology. 2017;22(8):484-92.
32. Wei Y., et al., High-dose dexamethasone vs prednisone for treatment of adult immune thrombocytopenia: a prospective multicenter randomized trial. Blood. 2016;127(3):296-302.
33. Neunert C., et al., The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood. 2011;117(16):4190-207.
34. Gotschalck MA., et al., Predictors for and outcomes after bone marrow biopsy in Scandinavian patients with chronic immune thrombocytopenia. Eur J Haematol. 2021;107(1):145-56.
35. Phatlhane DV., et al., The iron status of a healthy South African adult population. Clin Chim Acta. 2016;460:240-5.
36. Lawrie, D., L.M. Coetzee, and D.K. Glencross, Iron deficiency anaemia in healthy South African women despite iron fortification. SAMJ: South African Medical Journal. 2008;98:606-7.
37. Soto, A.F., P. Ford, and J. Mastoris, Thrombocytosis in Iron Deficiency Anemia: What the Primary Care Physician Needs To Know. Blood. 2006;108(11):3723-.
38. Huscenot T., et al., Iron deficiency, an unusual cause of thrombocytopenia: results from a multicenter retrospective case-controlled study. Ann Hematol. 2019;98(10):2299-302.
39. Ayalew GD., et al., Thrombocytopenia In Severe Anemia of Iron Deficiency. Blood. 2010;116(21):5153-.
40. Alabbood, M., M. Ling, and K. Ho, Glucocorticoid-induced diabetes among people without diabetes: a literature review. Practical Diabetes. 2018;35(2):63-7.
41. Costello RE., et al., Glucocorticoid use is associated with an increased risk of hypertension. Rheumatology. 2020;60(1):132-9.

**Appendices (In order of appearance)**

Appendix A: Haematology Patient Registry Consent Form

Appendix B: Human Research Ethics Committee Approval

Appendix C: Groote Schuur Hospital Approval

Appendix D: The South African Medical Journal – Author Guidelines

Appendix E: Data collection sheet

Western Cape Government
Health

Haematology Department, Groote Schuur Hospital
Main Road, Observatory, 7925

**Consent for patient information to be collected in the E5 Clinic Haematology Database**

What is the E5 Clinic Haematology database and what is it used for?

- The E5 Clinic Haematology database collects medical information from all patients with blood diseases in our clinic (E5 Clinic, E Floor, New Main Building, Groote Schuur Hospital, Observatory, Cape Town, 7925).
- This information is used to improve the service and the care delivered to you
- This database will record routine clinical data electronically rather than on paper to prevent information from being lost.
- The information is important for healthcare planning. It allows treaters and patients to negotiate and lobby with government and other care providers to improve services.
- We will collect information on demographics, medical history, diagnosis and treatment.

Will information about you be used for research?

Information from the database may be used to study haematological disorders, however ethical approval will be sought from the local ethics committee for this new research and all reports will use de-identified information to maintain your privacy.

How will your privacy and confidentiality be protected?

- The National Health Act of 2003 stipulates that medical records are kept confidential.
- All personal information will be password protected and encrypted in a secure database. Staff will have appropriate levels of access.

What are the risks of being included in the database?

- Personal information will be stored in the database however, all information will be secure and will not be accessible to anyone other than the relevant clinic staff.
- Personal identifiers will be retained to ensure accuracy of data as this is clinic database by which your treatment will be managed and delivered.

What are the benefits of being included in the database?

This database forms an integral part of the delivery of your day to day care and will be an important tool for improving the quality of patient care.

What rights do I have?

You may withdraw your consent to be included in the database at any time and request that some or all of your information is removed from the database.

**Informed consent form:**

I have been asked to participate in the E5 Clinic Haematology Database by the staff of this clinic. I have been given a chance to read the information sheet and to ask questions about the database. These questions have been answered to my satisfaction. I agree to participate in the database. I know that I can withdraw from the database at any time.

Patient sticker:

**The Database, including the above information, has been described to me orally. I understand what my involvement in the Database means and I voluntarily agree to participate.**

_____ _____

Name AND signature of patient Date

**In case of minors or under legal guardianship:**

_____ _____

Name AND signature of legal guardian **If patient unable to read or write:** Date

Thumb print

_____ _____

Name AND signature of witness **If patient needs a translator:** Date

_____ _____

Name AND signature of translator (Where applicable) Date

_____ _____

Name AND Signature of staff member Date

**UNIVERSITY OF CAPE TOWN**
**Faculty of Health Sciences**
**Human Research Ethics Committee**

**Room 45 E-52-E-Floor- Old Main Building**
**Groote Schuur Hospital**
**Observatory 7925**
**Telephone** [021] 406 6492
**Email:** hrec-submissions@uct.ac.za
**Website**: www.health.uct.ac.za/fhs/research/humanethics/forms

28 March 2022

**HREC REF: 197/2022**

**A/Prof E Verburgh**
Clinical Haematology
E-5 NGSH
Email: estelle.verburgh@uct.ac.za
Student: drdmapimhidze@gmail.com

Dear A/Prof Verburgh

**PROJECT TITLE: OUTCOME IN NEWLY DIAGNOSED IMMUNE THROMBOCYTOPENIA: A RETROSPECTIVE ANALYSIS OF A TERTIARY HAEMATOLOGICAL CENTRE IN SOUTH AFRICA-MASTERS CANDIDATE-DR DANAI MAPIMHIDZE-SUB-STUDY LINKED TO R024/2018**

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

**This approval is subject to strict adherence to the HREC recommendations regarding research involving human participants during COVID -19, our letter dated 02 February 2022 provides guidance found on our website:**
**http://www.health.uct.ac.za/fhs/research/humanethics/forms**

**Approval is granted for one year until the 30 March 2023.**

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

***The HREC acknowledge that the student: Dr Danai Mapimhidze will also be involved in this study.***

**Please quote the HREC REF 197/2022 in all your correspondence.**

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval, where necessary, before the research may occur.

Yours sincerely

**PROFESSOR M BLOCKMAN**
**CHAIRPERSON FACULTY OF HEALTH SCIENCES HUMAN RESEARCH ETHICS COMMITTEE**
Federal Wide Assurance Number: FWA0000163 7Institutional Review Board (IRB) number: IRB00001938 NHREC-registration number: REC-210208-007
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2020), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Declaration of Helsinki (2013) guidelines. The Human Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Western Cape Government

**GROOTE SCHUUR HOSPITAL**
**Enquiries**: Dr Bernadette Eick
**e-mail**: ~~GSHReserach.Request@westerncape.gov.za~~

**PROFESSOR ESTELLE VERBURGH**
MEDICINE: HAEMATOLOGY
E-mail: estelle.verburgh@uct.ac.za

Dear Professor Verburgh

**RESEARCH PROJECT: Outcome in a newly diagnosed Immune Thrombocytopenia: A Retrospective Analysis of a Tertiary Haematological Centre in South Africa_Masters candidate: Dr Danai Mapimhidze**

Your recent letter to the hospital refers.

You are granted permission to proceed with your research, which is valid until **30 March 2023.**

Please note the following:

a) Your research may not interfere with normal patient care.
b) Hospital staff may not be asked to assist with the research.
c) **Confidentiality must always be maintained.**
d) No additional costs to the hospital should be incurred as indicated in your Annexure 2 i.e. Lab, consumables or stationery. **If access to TRACK Care/NHLS is required, kindly attach our letter of approval to the application form and approach Information Management to assist with data.**
e) **No patient folders may be removed from the premises or be inaccessible.**
f) Please provide the research assistant/field worker with a copy of this letter as verification of approval.
g) **Should you at any time require photographs of your subjects, please obtain the necessary indemnity forms from our Public Relations Office (E45 OMB or ext. 2187/2188).**
h) Should you require additional research time beyond the stipulated expiry date, please apply for an extension.
i) Please discuss the study with the HOD before commencing.
j) Please introduce yourself to the person in charge of an area before commencing.
k) On completion of your research, please forward any recommendations/findings that can be beneficial to use to take further action that may inform redevelopment of future policy / review guidelines.
l) If the researcher is not GSH staff member, a supernumerary contract is required before commencement of the research.
m) Please contact Michelle Riley (Patient Fees) at ext. 2276 to ascertain if there will be charges for conducting the Research and to obtain a quote or to discuss charges
n) **Kindly submit a copy of the publication or report to this office on completion of the research.**
o) **At no time should any posters encouraging patients to partake in research, be displayed within a clinical area.**
p) **Please adhere to ALL COVID-19 regulations and Groote Schuur Hospital policies.**

I would like to wish you every success with the project.

Yours sincerely

**DR BERNADETTE EICK**

**CHIEF OPERATIONAL OFFICER**
**Date:** 14 April 2022

C.C. Mr. L. Naidoo, Prof. N. Ntusi, Prof. V. Louw, Mr. A. Mohamed, Dr. N. Khumalo



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**General article format/layout**

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General: • Manuscripts must be written in UK English.

- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).
- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

*SAMJ* is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:

- Human Gene Mapping Workshop (HGMW): genetic notations and symbols
- HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
- OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions

- Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

**Research**

*Guideline word limit: 4 000 words*

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text. Do not replicate data in tables and in text .

*Structured abstract*

- This should be 250-400 words, with the following recommended headings:

- **Background:** why the study is being done and how it relates to other published work.
- **Objectives:** what the study intends to find out
- **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data. o **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study. o **Conclusion:** must be supported by the data, include recommendations for further study/actions.

- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

*Main article*

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, gender, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

*Results*

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

*Discussion*

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

*Conclusions*

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

**Data collection sheet**

- Date of birth: YYYMMDD
- Sex: male, female
- Date of ITP diagnosis: YYYMMDD
- Presenting symptoms
- Critical Bleeding: yes, no
- Asymptomatic: yes, no
- Blood results at diagnosis, where available
- Hb: numerical value
- Platelets: numerical value
- Hepatitis B: negative, positive, unknown
- Hepatitis C: negative, positive, unknown
- HIV status: negative, positive, unknown
- ANA: negative, positive, unknown
- Ferritin levels: numerical value
- Bone marrow performed: yes, no
- The presence of comorbidities at the time of diagnosis:
- Hypertension: yes, no
- Diabetes: yes, no
- Iron deficiency anaemia: yes, no
- 1st line Treatment type o Prednisone 0.5-2 mg/kg/d orally only o Dexamethasone 40 mg intravenous pulse for 4 days only o Prednisone & Dexamethasone
- Platelet response to treatment:
    - Complete response o Partial response
    - No response, defined as a platelet count of less than 30; or less than doubling of the platelet count
- Relapse: yes, no
- Side effects from therapy administered
- Hypertension: yes, no
- Diabetes: yes, no

- ITP related morbidity at any time point: yes, no
- Classification of patients at last follow up o In Remission after 1st line treatment o Persistent ITP – defines ITP lasting 3-12 months following diagnosis; patients with PR/NR requiring treatment 3-12 months into diagnosis fall into this category o Chronic ITP - defines ITP lasting more than 12months post diagnosis; patient with PR/NR requiring treatment more than 12 months into treatment fall into this category o Death