Transfusion Practices in the Eastern Cape Province of South Africa in the era of HIV and HAART.

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DECLARATION:

I, Karin van den Berg, ID Number 69112 0013 083, certify that the dissertation hereby submitted by me for the M.M.Clin.Sc. (Transfusion Medicine) degree at the University of the Free State is my independent effort and had not previously been submitted for a degree at another university/faculty. I furthermore waive copyright of the dissertation in favour of the University of the Free State.

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DEDICATION AND ACKNOWLEDGEMENTS:

Dedication

This study is dedicated to my husband, Wayne Ingram, and my children, Zania and Divan, who provided me with the love and support without which I would not have been able to undertake a project of this nature. I am eternally grateful for being forgiven for missing so many family events and commitments, but believe that my children will learn to value the power of an excellent education.

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- The patients of the Livingstone Hospital whose files I reviewed for this study.

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LIST OF ACRONYMS

ACD	Anaemia of chronic disease
AIDS	Acquired immune deficiency syndrome
AIHA	Autoimmune haemolytic anaemia
ART	Anti-retroviral therapy
AZT	Zidovudine
DAT	Direct anti-globulin test
DoH	Department of Health
DPDF	Discharge patient data form
EXCO	Executive Committee
FBC	Full blood count
FFP	Fresh frozen plasma
GIT	Gastro-intestinal tract
Hb	Haemoglobin
Hct	Haematocrit
HIV	Human immunodeficiency virus
HREC	Human Research and Ethics Committee
ICU	Intensive care unit
MCV	Mean corpuscular volume
PCS	Patient Control Sheet
PEPFAR	United States President's Emergency Plan for AIDS Relief
QoL	Quality of life
r-HuEPO	Recombinant human erythropoietin

RBC	Red blood cell
RCC	Red cell concentrate
SANBS	South African National Blood Service
TMA	Thrombotic microangiopathy
TPDF	Transfused patient data form
TTP	Thrombotic thrombocytopenic purpura
UFS	University of the Free State
USA	United States of America
WHO	World Health Organisation
WPBTS	Western Province Blood Transfusion Service
WSU	Walter Sisulu University

KEY WORDS

1. Blood transfusion
2. HIV/AIDS
3. Hospitalised patients
4. Anaemia
5. Antiretroviral drugs
6. CD4 Count
7. Audit of transfusion practices
8. Blood utilisation
9. In-hospital mortality
10. Eastern Cape public health sector

SUMMARY

Background and introduction:

The HIV/AIDS pandemic has irrevocably changed the face of healthcare delivery and research. This is especially true in South Africa with its estimated 5.26 million HIV-infected people. It was not until the significant up scaling of the anti-retroviral therapy roll-out that the HIV-incidence rate in South Africa started declining substantially from an estimated 1.32% in 2005 to an estimated 0.85% in 2013. Cytopaenias are common in HIV-infected individuals. Their risk of developing anaemia ranges from 60 to 95% during the course of the disease. The impact of HIV/AIDS on blood utilisation in the country is largely unknown. With this study we aimed to address the lack of knowledge regarding the blood requirements of the HIV-positive population and how the changing epidemic may affect future blood utilisation, by establishing what proportion of blood issued to medical and surgical patients admitted to a large referral hospital in the Eastern Cape Province of South Africa, was issued to HIV-positive patients

Methods

We conducted a retrospective cross-sectional study analysing the prevalence of HIV among patients receiving blood and blood products. Baseline demographic data was collected on all patients admitted during a three-month period with additional clinical data collected on patients who received a blood transfusion.

Ethics approval was obtained from the UFS and the South African National Blood Service (SANBS). Approval to complete the study was obtained from the senior management of the Hospital and the local blood service offices. Following a short pilot study during which the various systems were tested, data collection commenced on 7 January 2013 and was completed on 6 April 2013.

Results

A total of 3438 patient admissions were included in the study with equal distribution between male and female patients. Patients tended to be younger with almost 75% of patients younger than 60. Almost 8% of patients were transfused. HIV status was poorly recorded. Only 25% of patients had a HIV test result on file. The reported HIV prevalence was 14%. The median LOS was 7 days and in-patient mortality 8%.

During 330 transfusion episodes, 267 patients received 609 units of RBC, i.e. 1.24 transfusion episodes per patient. Except for 6 units, all units issued were recorded as transfused, translating to a transfused ratio of 1.00:0.99. Being HIV-positive, surgical admissions, having been admitted to ICU, extended LOS and death at discharge were independently association with having received a transfusion. Mean pre- and post-transfusion Hb levels were significantly lower in HIV-positive patients and these patients were less likely to have had a

correctly completed consent form on record, but were more likely to have had their anaemia investigated.

Discussion

The complex HIV-testing at this facility hampered the analysis of the data and raises serious public health questions. Despite this, it is clear that HIV significantly impacts blood utilisation at this facility. HIV-prevalence among all admissions was found to be ~ 14%, as compared to the almost 20% among the recipients of blood. Similarly 26% of the transfusion episodes involved HIV positive patients. However, only 16% of the units issued were issued to HIV-positive patients.

The data suggests that HIV-status significantly influenced doctors' transfusion practices. HIV-positive patients had significantly lower pre- and post-transfusion Hb levels suggesting lower transfusion triggers and targets for HIV-positive patients. These patients were also less likely to have had correctly completed consent forms; only a third of HIV-positive patients had correctly completed forms on record.

Conclusion

HIV contributes significantly to the blood utilisation at a tertiary hospital in the Eastern Cape and would appear to influence clinicians' transfusion practice.

The exact nature of the interaction between HIV and transfusion requires further investigation.

OPSOMMING

Agtergrond en inleiding

Die MIV-VIGS pandemie het oor die laaste 30 jaar 'n ingrypende inpak op elke aspek van gesondheidsdienslewering gehad. Suid-Afrika, met sy geraamde 5.26 miljoen MIV-geïnfekteerde mense, is geen uitsondering nie. Die eksponensiële groei in die MIV-epidemie is eers met die grootskaalse uitrol van antivirale middels, 'n knou toegedien. Dit het gelei tot 'n noemenswaardige daling in die MIV-insidensie van 'n beraamde 1,32% in 2005 tot 'n beraamde 0,85% in 2013.

Sitopenieë is algemeen onder MIV-geïnfekteerde individieë. Geïnfekteerde individue het 'n 60-95% risiko om anemie te ontwikkel gedurende die verloop van hul siekte. Ten spyte hiervan is die impak van die MIV-VIGS epidemie op die gebruik van bloed grootliks onbekend. Hierdie studie het ten doel gehad om die gebrek aan kennis rakende die algemene bloedbenodighede van die MIV-positiewe populasie en hoe die verandinge in die epidemie laasgenoemde beïnvloed, aan te spreek. Ons het beoog om vas te stel watter persentasie bloed wat aan pasiënte in a groot verwysingshospitaal in die Oos-Kaap Provinsie van Suid-Afrika uitgereik was, was aan MIV-positiewe pasiënte uitgereik.

Studiemetodiek

Ons het ‘n retrospektiewe, deursnee-studie van die MIV-prevalensie onder patiënte wat bloed en bloedprodukte ontvant het, gedoen. Basiese demografiese inligting is op alle patiente wat wat oor ‘n 3-maande periode toegelaat is, ingewin. Addisionele kliniese inligting is versamel op pasiënte wat bloed tydens die studieperiode ontvang het.

Na verkryging van etiese toestemming vanaf die etiekkommittees van die Universiteit van die Vrystaat asook die Suid Afrikaanse Nasionale Bloeddiens, is operasionele toestemming van die senior bestuur van die hospitaal en lokale bloeddienskantore verkry. Na afloop van ‘n loodsstudie waartydens die verskillende sisteme getoets is, is dataversamleing op 7 Januarie 2013 begin. Datavernsameling is op 6 April 2013 voltooi.

Studie-resultate

In totaal is 3438 pasiënttoelatings by die studie ingesluit. Daar was ‘n gelyke verspreiding tussen manlike en vroulike pasiënte. Die pasiëntpopulasie was jonger met amper 75% van die pasiënte jonger as 60 jaar. Ongeveer 8% van die pasiënte was getransfuseer. HIV-status was grotendeels onbekend en slegs vir 25% van pasiënte gedokumenteer. Die gerapporteerde HIV-prevalensie was 14%. Die mediane duur van toelating was 7 dae en die binne-pasiënt mortaliteitsyfer 8%.

Gedurende 330 transfusie-episodes, het 267 pasiënte 609 eenhede rooibloedselle ontvang, met dus 1.24 transfusie-episodes per pasiënt. Behalwe vir 6 eenhede was alle uitgereikte eenhede as getransfuseer aangeteken. Dit verteenwoordig 'n uitreik tot transfusie verhouding van 1.00:0.99. MIV-positiviteit, chirugiese toelating, toelating tot die intensiewe sorgeenheid, verlengde duur van toelating en dood met ontslag was onafhanklik geassosieer met die ontvangs van 'n transfusie. Die gemiddelde voor- en na-transfusie Hb-vlakke was betekenisvol laer in MIV-positiewe pasiente en hulle het minder gereeld korrek voltooide toestemmingsvorms op lêer gehad, maar was meer dikwels verder vir die oorsaak van hulle anemie ondersoek.

Bespreking

Die gekompliseerde HIV-toetsing by die hospitaal het die data-analise beinvoed en het ernstige publieke gesondheidsorgvrae na vore gebring. Ongeag hiervan, was dit duidelik dat MIV bloedgebruik beduidenisvol beïnvloed. Die totale MIV-prevalensie was ongeveer 14% teenoor byna 20% onder die getransfuseerde pasiënte. MIV-positiewe pasiënte was by 26% van die transfusie-episodes betrokke, maar het slegs 16% van die uitgereikte eenhede ontvang.

Die data dui daarop dat MIV-status dokters se transfusiepraktyke beïnvloed. MIV-positiewe pasiënte het betekenisvolle laer voor- en na-transfusie Hb-

vlakke gehad, en was ook minder geneig om korrek voltooide toestemmingsvorms op lêer te hê. Slegs ‘n derde van getransfuseerde MIV-positiewe pasiënte het korrek voltooide vorms gehad.

Gevolgtrekking

MIV dra betekenisvol by tot die bloedverbruik by hierdie tersiêre hospitaal en blyk om dokters se transfusiepraktyke te beïnvloed. Die spesifieke interaksie tussen MIV en bloodtransfusie behoort verder ondersoek te word.

CHAPTER 1: ORIENTATION TO THE STUDY

1.1 Introduction

HIV/AIDS has profoundly impacted healthcare delivery across the globe. Nowhere is this more evident than in South Africa which has one of the biggest epidemics in the world. There is probably no other disease that has been the focus of so much research and healthcare policy development as HIV/AIDS. Whereas the impact of the pandemic on blood collection has been studied extensively by the various blood transfusion services internationally, its impact on blood utilization is largely unknown. Furthermore, both the fields of Transfusion Medicine and HIV-care are changing continuously, with various research areas in each field resulting in an ever growing body of evidence on these two specialized clinical fields.

Doctors of all disciplines are continuously confronted with issues pertaining to these fields, yet, especially Transfusion Medicine does not form a significant part of the under- or postgraduate training of the majority of clinicians in South Africa. Thus, the management of the transfusion needs of patients is often taught through anecdotal instruction from senior doctors to their junior counterparts, raising concerns that clinicians may be potentially inappropriately differentiating the transfusion care provided to HIV-positive patients as compared to that afforded to HIV-negative patients.

It is for these reasons that we conducted this study analysing the impact of HIV/AIDS on the blood utilization of a large tertiary referral hospital in the Eastern Cape Province of South Africa. In addition, we assessed whether HIV/AIDS influenced the transfusion practices of the attending clinicians, with the view of providing the hospital and blood transfusion service management with scientific information that will aid their business and financial planning for the future.

1.2 Problem statement

The problem we aimed to address in this study is the lack of knowledge regarding the overall blood requirements of the HIV-positive population and in particular, to determine what proportion of blood is being issued to HIV-positive patients and whether a doctor's application of good transfusion practices are influenced by the patient's HIV status.

1.3 Overall goal of the study

The overall goal was to determine the prevalence of HIV-positivity among the recipients of blood and blood products. Secondary goals included establishing the level of adherence to good transfusion practices; whether it was influenced by HIV-status and among which clinical specialities the patients who received blood and blood products were distributed.

1.4 Aim of the study

We aimed to establish what proportion of blood issued to medical and surgical patients admitted to a large referral hospital in the Eastern Cape Province of South Africa was issued to HIV-positive patients and whether HIV status influenced the doctors' adherence to good transfusion practice. The third aim of this study was to describe the distribution of the clinical specialities in which the recipients of blood and blood products were admitted.

1.5 Objectives of the study

The objective of this research was to study the prevalence of HIV amongst patients receiving blood at a large public sector referral hospital in Port Elizabeth in the Eastern Cape Province of South Africa and to review whether a patient's HIV status influenced doctors' transfusion practices habits. The study included a secondary comparison analysis of the distribution of clinical specialities among which the recipients of blood and blood products were admitted. In addition, we aimed to analyse the pre- and post-transfusion haemoglobin levels as well as the indications for transfusion.

As part of the process of developing and conducting the study we aimed to cover the following objectives:

- Gain an understanding of the extent of the HIV pandemic and how it influences clinical care in South Africa, in particular how it affected health

resource utilisation such as bed occupancy and displacement of HIV-negative patients. This was done through a literature review.

- Review and analyse the current overall blood utilisation in South Africa and how it had changed over time, specifically to assess whether changes in national blood utilisation followed the trends of the HIV epidemic. This was done through a literature review.

- Develop a deeper understanding of anaemia in HIV, in particular regarding the pathophysiology, causes, investigation and management. The aim was to understand whether there would be any reason for managing and transfusing HIV-positive patients differently to those who are HIV-negative. This was done through a literature review.

- Gathered information on the transfusion practices of doctors in relation to both HIV-positive and negative patients to evaluate the appropriateness of their care, with the aim of identifying areas of inappropriate care for which training and education can be developed. This aim was achieved through the collection of data to address the following research questions:
    - What percentage of blood is issued to HIV-positive patients?
    - Do doctors have different transfusion triggers for HIV-positive patients?

- Do doctors have different transfusion targets for HIV-positive patients?
- Do doctors provide clear indications for the transfusion on the blood requisition form?
    - Are the indications recorded on the blood requisition form?
    - Are the indications recorded in the patient's file?
    - Do the indications for transfusion on the blood requisition form differ from those recorded in the patient's file?
    - Do the indications differ between HIV-positive and –negative patients?
- Do doctors check post transfusion haemoglobin (Hb) or haematocrit (Hct)?
- Do doctors obtain informed consent prior to transfusing patients?
    - Are they more or less likely to take consent from HIV-positive patients compared to HIV-negative patients?
- Do doctors establish the underlying cause of the anaemia?
    - Are the appropriate investigations performed prior to commencing the transfusion?
    - Is a final diagnosis recorded?

Being able to demonstrate what proportion of blood is being issued to HIV-positive patients will provide us with the first step in understanding the impact of HIV/AIDS on blood utilisation. In addition it will begin to address some of

the knowledge gaps that will assist health authorities and blood bankers to better plan health resource, in particular blood and blood product, allocation.

1.6 Scope of the study

This study was conducted in the fields of blood transfusion and HIV care as a cross-sectional epidemiological survey. The focus was on establishing the prevalence of HIV among recipients of blood and blood products and its impact of the transfusion practices of doctors. The study was performed in the various medical and surgical wards at a large, public-sector, referral hospital in the city of Port Elizabeth in the Eastern Cape Province of South Africa

1.7 Value of the study

Being able to describe the prevalence of HIV among blood recipients, will aid in better understanding its impact on health resources in general. More specifically, it will assist the various health authorities as well as the blood transfusion services to plan and allocate appropriate resources to ensure a safe and sufficient blood supply for the nation.

Better understanding of current transfusion habits will inform future training and education requirements to ensure that doctors utilise this scarce resource in a rational and evidence-based manner. However, the investigator is aware that establishing the prevalence of HIV among the recipients of blood is only

the first step in fully understanding the impact of HIV/AIDS on blood utilization.

1.8 Research design

We conducted a cross-sectional study analysing the prevalence of HIV among patients receiving blood and blood products. The study was conducted over a three-month period from 7 January to 7 April 2013.

With this study, the researcher aimed to improve the understanding of the impact of HIV/AIDS on the blood requirement of the country at a macro level, but also at the level of individual hospitals and how the changing epidemic in South Africa, including the introduction of anti-retroviral therapy, may impact blood utilisation, both nationally as well as locally.

The study was performed at Livingstone Hospital, a tertiary referral hospitals in the Eastern Cape Province of South Africa. Using various data collection tools, data were collected on all patients admitted to the hospital over a three-month period. Additional data was collected on those patients who received blood transfusions. The data was analysed using standard statistical analysis, including summary statistics, bivariate analysis as well as multivariate logistical regression modeling.

1.9 Implementation of the findings

The findings of this research will be presented locally to the management of the Port Elizabeth Hospital Complex, but also to the Provincial Department of Health, and where possible, the National Departments of Health, to inform future budgetary decision making in relation to blood products, but also in relation to the learning and development needs of doctors prescribing blood and blood products. In addition, the findings will be presented to the SANBS and the Western Province Blood Transfusion Service (WPBTS) to assist in the long-term business planning to meet the country's blood needs.

The researcher aims to submit abstracts to appropriate national and international congresses as well as manuscripts for publication in peer-reviewed academic journals so as to raise awareness of the issues identified and addressed through this research and thereby aiding in the appropriate utilisation of what is a scarce and costly resource.

1.10 Arrangement of the thesis

This study will be reported as follows:

In Chapter 1, ***Orientation to the study***, the background to the study is provided, the major themes that will be explored are described, the research problem is stated and the overall goal and objectives clarified. Furthermore, the scope of the study as well as its value and significance is explained. The reader is introduced to the research methods that were employed and these

are briefly explained. This chapter should provide the reader with an overview of what the dissertation contains.

In Chapter 2, ***The HIV pandemic and its impact on health resource utilization***, the changes in the HIV pandemic are explored. Specific attention is paid to the progression of the epidemic in South Africa, known to have one of the largest epidemics in the world. Attention is drawn to the impact of HIV/AIDS on health resource utilization and the financial burden the epidemic has placed on the country.

In Chapter 3, ***Anaemia in HIV and the role of blood transfusion***, the clinical aspects of HIV, in particular the various cytopaenias associated with HIV and how it may impact blood utilisation is reviewed. The association between anaemia and HIV-disease progression and HIV-associated morbidity and mortality is described and how interventions that address HIV-disease progression, such as an effective anti-retroviral therapy (ART) program, may impact HIV-associated anaemia and therefore potentially, blood utilisation.

In Chapter 4, ***Research design and methodology***, the type of study, the study sample and the data collection methods are described. Particular attention was paid to the describing of potential measurement errors, bias and confounding and how these were avoided. The nature of the pilot study and the relevant ethical considerations are explained.

In Chapter 5, ***Research Findings***, the results of the research are reported and described. Appropriate tables and figures are used to provide additional detail and to clarify certain concepts deemed to be of greater importance.

In Chapter 6, ***Discussion***, the findings of the research is placed in context and further clarified. The main themes resulting from the data analysis is further explored in this section.

In Chapter 7, ***Conclusions, limitations and recommendations***, the most important conclusions, limitations and recommendations are discussed.

1.11 Conclusion

Chapter 1 focussed on providing the reader with an introduction and background to the research undertaken and to place it in to context within the fields of HIV and Transfusion Medicine. The research question or problem was defined and the overall goal and objectives clarified. The reader was also provided with the structural arrangement of the dissertation.

In the next chapter, Chapter 2, entitled ***The HIV pandemic and its impact of health resource utilisation,*** a review of the literature pertaining to the size of the HIV pandemic and the resultant impact on health resource utilisation is presented.

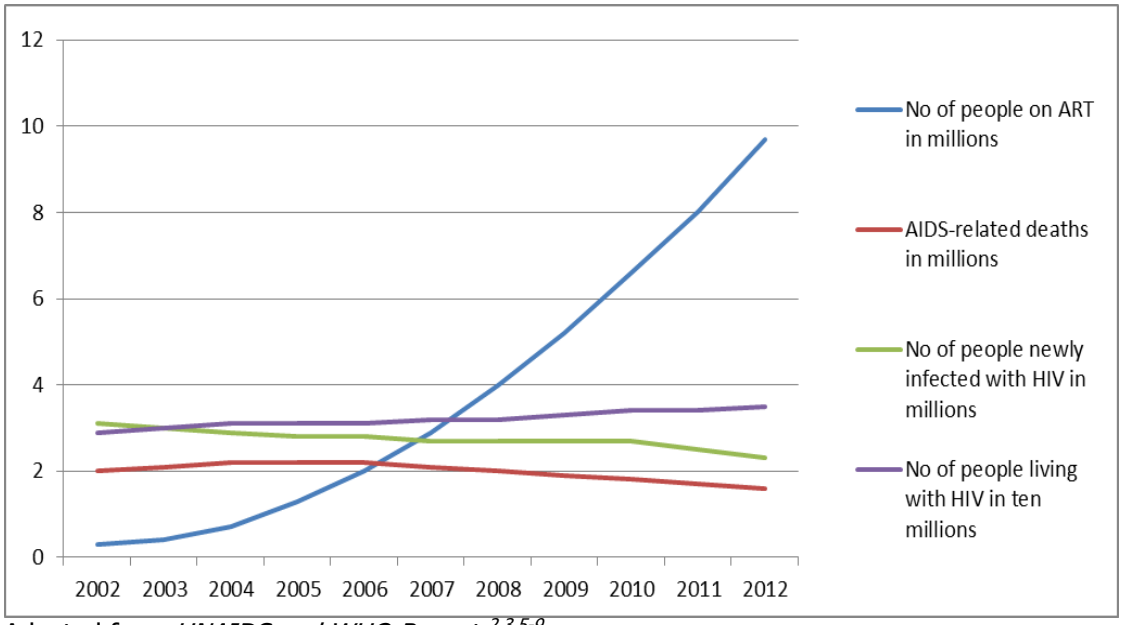
CHAPTER 2: THE HIV PANDEMIC AND ITS IMPACT ON HEALTH RESOURCE UTILISATION

2.1 HIV/AIDS: A changing epidemic

The HIV/AIDS pandemic has irrevocably changed the face of healthcare delivery and research. HIV is arguably the most researched disease and organism of all times, yet remains one of the leading causes of death in Africa. By the year 2000, less than twenty years after its identification, HIV/AIDS related deaths surpassed malaria as the leading cause of death in Africa.[1] On a global scale, it is estimated that by 2012 around 35 million people were living with HIV/AIDS, of whom 10% were children younger than 15 years of age.[2] The 2011 UNAIDS HIV/AIDS progress report[3] showed an estimated 15% decrease in incident (new) HIV infections, however, there was still an alarming 2.7 million (estimated) new infections during 2010 globally.

Of note is the apparent significant decline in HIV prevalence among young people, with an estimated 32% decrease in prevalence among a group of 24 mostly low and medium development index countries, with a national HIV prevalence of 1% or higher.[3] However, large regional variances were found with some countries showing an up to 50% reduction in prevalence, while others showed no decline.[3] Similar trends were identified in HIV/AIDS related death rates, with fewer people dying due to HIV/AIDS related causes. By 1999 it was estimated that a total of 18,8 million HIV/AIDS related deaths had occurred during the course of the epidemic with an estimated 2,8 million

deaths in 1999 alone.[4] However, recent estimates suggest a decline from 2,2 million deaths in 2005 to an estimated 1,8 million in 2010.[3] It is important to recognize that with continued downward trends in AIDS related deaths, the number of people living with HIV/AIDS will continue to increase, heralding a new set of public health challenges which will require innovative approaches and management (Figure 1).



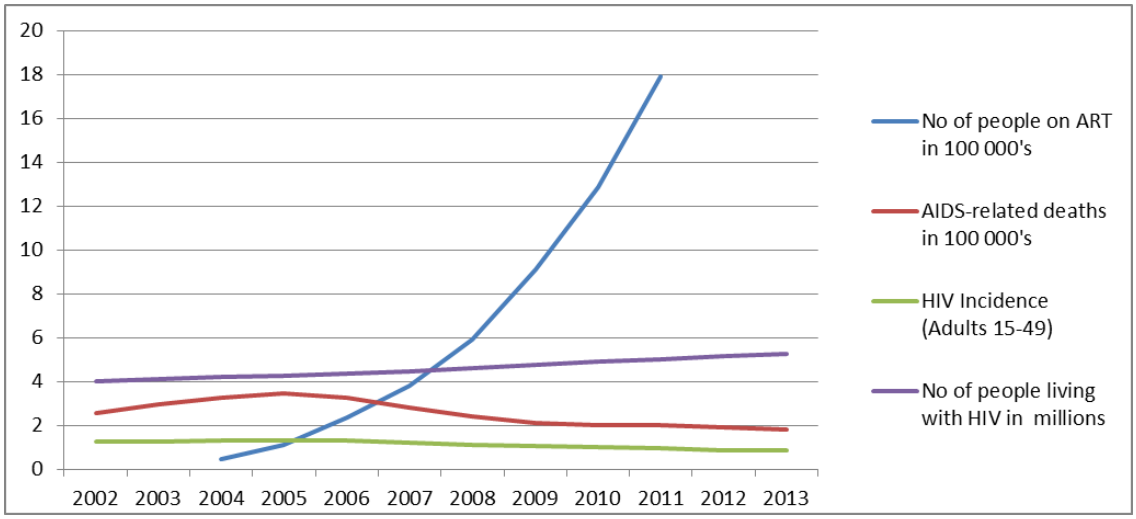
Adapted from *UNAIDS and WHO Reports*[2,3,5-9]

Figure 1: Change in the global HIV epidemic, 2002 to 2012

2.2 HIV/AIDS in South Africa

It is a well-established fact that the South African HIV/AIDS epidemic is the largest in the world, contributing approximately 17% of the total number of HIV infected persons globally, despite having only 0.7% of the world population.[5,10,11] The size of the epidemic in South Africa is greater than that

of all of Asia combined, with an estimated 5,26 million people currently infected in South Africa.[3,12] In addition to the size of its epidemic, South Africa has not shown a similar significant downward trend in its HIV-related epidemiological data as seen in other countries or regions. With an annual incidence rate of around 0.85%[12], South Africa's massive contribution to the extent of the pandemic is likely to continue for the foreseeable future (Figure 2).



Adapted from *Mid-year population estimates 2011: Global HIV/AIDS response: Epidemic update and health sector progress towards Universal Access. Progress Report 2011* and various STATSA reports[12-15]

Figure 2: Change in the South African HIV epidemic, 2002 to 2013

In the book "HIV/AIDS in South Africa"[13] Dr Mark Colvin writes: "There is a scarcity of data on the impact of HIV on health care services with most of it coming from small cross-sectional studies. Even the longitudinal data tends to be focused on specific wards and with no large-scale studies published; there are few data on the impact on health services more broadly". HIV/AIDS

research and care are mainly funded by the public sector, often through programs such as the United States President's Emergency Plan for AIDS Relief (PEPFAR) and The Global Fund to Fight AIDS, Tuberculosis and Malaria.[3] This, in synergy with the rapid and massive civil society involvement in HIV/AIDS have led to a growing demand for co-ownership of research and a commanding voice in policy development, a *"necessary synergy between activism and science".*[14]

In addition, there was a massive influx of donor funding after 2004, reaching values in excess of US$10 billion in 2007.[15] This has enabled the funding of care of millions of people living with HIV/AIDS, yet more than 50% of people eligible for anti-retroviral therapy (ART) still do not have access to care.[15] However, this influx of donor funding has heralded a change from an emergency response to a more long-term sustained effort towards the management of HIV/AIDS.[15-17]

Despite the significant increase in the funding of both HIV/AIDS research and care, it remains the leading cause of morbidity and mortality in Sub-Saharan Africa, and the full impact of this disease on a macro- and micro-economic level, including health care utilisation and redistribution, remains unclear. More recently, in a 2009 review article on the impact of HIV on human development in African countries, Boutayeb noted that HIV/AIDS had long since ceased being only a health sector crisis, but constituted a development

question, impacting on all aspects of human security and human development, particularly so in Sub-Saharan Africa.[18] By 2006, the life expectancy in South Africa had fallen to 51 years of age[8], and importantly, most South African adults were dying during the economically active years of their life. Midyear population estimates in 2013, suggest that life-expectancy has improved to 59.6 years at birth. Even though causal relationship was not documented, it is clear that AIDS-related deaths during the same period fell from 324 192 to 178 373 and coincides with the large-scale roll-out of antiretroviral therapy. In South Africa, as in other developing countries, the loss of the economically active population is particularly devastating, given the long established culture of this particular group financially supporting extended families, often widely dispersed in rural areas.[4] While acknowledging the human and economic development impact of the epidemic in South Africa, the main focus of this manuscript is its impact on health care and health care utilisation.

On a micro-economic level, it has long since been established that both the direct and indirect cost of care for HIV-positive patients significantly exceeds those of HIV-negative patients. As far back as 1988, Hassig *et al.* demonstrated a significantly higher cost of care, both direct and indirect, for HIV-positive patients compared to HIV-negative patients in Kinshasa, in what is now the Democratic Republic of the Congo.[19] These findings were echoed by similar studies from the United States.[20,21] It has been noted that the

displacement of HIV-negative patients by their HIV-positive counterparts may have, in fact, affected the mortality rate of HIV-negative patients, probably due to the delayed admission of the HIV-negative patients, when conditions which generally would have been infinitely treatable, have deteriorated to the point where mortality become imminent.[19]

In addition to incurring higher cost of care than HIV-negative patients, HIV-positive patients have been shown to dominate bed-occupancy in those countries with high prevalence epidemics. The shift from an HIV infection epidemic in South Africa to that of an AIDS care one has been well documented. In 2001, Colvin *et al.*, showed that in a tertiary referral hospital in KwaZulu-Natal, at least 54% of all admissions to the adult medical wards were HIV positive and of those, 84% had AIDS.[22] Similarly, Pillay *et al.* found that 62% of paediatric admissions to the King Edward Hospital were HIV positive.[23] Several epidemiological studies during the late 1990's indicated a high prevalence of HIV among hospital in-patients in Sub-Saharan Africa as well as in South Africa, even among surgical and psychiatric patients.[24-28] HIV-positive patients were shown to have extended lengths of stay compared to their HIV-negative counterparts and was more likely to have had repeated admissions.[26] These findings were replicated in paediatric wards, although usually limited to infants, a finding probably related to the high mortality rate among HIV-positive infants.[23,29] Of particular note has been the consistent finding that HIV-positive inpatients tended to be younger, have a greater

mortality rate and higher rates of tuberculosis than inpatients admitted for non-HIV-related conditions.[13,22,23] Some later studies performed among surgical patients during the early half of the first decade of this century showed HIV prevalence rates of between 32% and 39%.[30,31] Even though we have not been able to find more recent reports on HIV/AIDS related bed occupancy, there has been nothing to suggest that these trends would have changed in any significant manner.

From the above discussion it is clear that there is a direct relationship between HIV/AIDS and health resource utilisation in general and hospitalisation in particular, but is has not been established whether there may also be such a relationship between HIV/AIDS and the utilisation of blood and blood products. Blood and blood products are still the conventional treatment of severe cytopaenias and so one has to review the role of cytopaenias in HIV to assess how HIV may affect blood utilisation.

2.3 Conclusion

This chapter focused on the global trends in the HIV pandemic and the changes in the prevalence and incidence across the globe. Similarly, the changes in the South African epidemic was explored and reviewed against global trends. The lack of a substantial reduction in the incidence and prevalence of HIV in South Africa was noted.

The impact of HIV on life expectancy and health resource utilisation was discussed, noting the higher cost of care, greater bed occupancy and displacement of HIV-negative patients from hospitals. In addition, it was established that HIV-positive in-patients tended to be younger, have a greater mortality rate and higher rates of tuberculosis than inpatients admitted for non-HIV-related conditions.

The next chapter, Chapter 3, focusses on reviewing the key issues related to anaemia in HIV, the prevalence and causes thereof, as well as the impact of early diagnosis and management. This is then reviewed in the context of the role of blood transfusion in HIV.

CHAPTER 3: ANAEMIA IN HIV AND THE ROLE OF BLOOD TRANSFUSION

3.1 Anaemia in HIV

Cytopaenias are common in the HIV-infected population.[32-34] Anaemia is the most common haematological abnormality found in HIV. It may occur at any stage of the disease and its prevalence and severity increases as the disease progresses.[33,34] It is estimated that 63-95% of HIV infected individuals will develop anaemia during the course of their disease.[33-35] It has also been shown to be an independent risk factor for mortality and that reversal of anaemia improves mortality rates, even after controlling for confounding factors such as CD4 count.[36,37] Anaemia in HIV, as in other chronic diseases, is associated with reduced quality of life (QoL) and its resolution with significant improvement in QoL.[38,39] In particular, patients reported improvement in physical functioning and in energy/fatigue scales, factors known to be affected by HIV status, independent of the presence of anaemia. In an open-label study in 1994, Revicki *et al.* demonstrated significant changes in energy levels and concomitant increases in health perceptions and satisfaction with health in patients with AIDS who responded to recombinant human erythropoietin (r-HuEPO) for the treatment of their anaemia.[40] The beneficial effects of resolution of anaemia are not limited to those with AIDS, but extend to patients with earlier stages of HIV disease.[41] In contrast, HIV-positive anaemic patients, not only demonstrated poorer QOL assessments, but were also noted to have higher health resource utilisation scores.[42]

The early diagnosis and prompt management of anaemia in the setting of HIV is not only important to improve clinical outcomes and QoL, but can play an important role to reduce health resource utilisation. However, to do this, requires a good understanding of the pathophysiology of anaemia in HIV. The causes of anaemia in HIV are multifactorial, often overlapping and occurring simultaneously in the same patient. It may be the result of either the direct or indirect effects of the HIV infection and can affect both the production as well as the destruction/survival of red blood cells. HIV may affect erythropoiesis directly through infection of red cell precursors and bone marrow stromal cells, as well as through the release of cytokines. These factors contribute to the development of anaemia of chronic disease (ACD) and are likely responsible for the majority of cases of anaemia in HIV-positive patients, who would usually present with a moderate, normochromic, normocytic anaemia.[34] ACD is associated with inappropriately low erythropoietin levels (compared to the degree of anaemia), a suppressed reticulocyte response and defective iron metabolism.

Anaemia may also be the result of the indirect effects of HIV infection. Common among these are the nutritional deficiencies as a result of the anorexia, malabsorption and metabolic disorders associated with HIV. With disease progression, opportunistic infections, neoplasms, infiltrative and infective bone marrow conditions and drug interactions increase in importance

as the causes of anaemia in HIV. Among the opportunistic infections which can lead to profound anaemia is parvovirus B19 infection, which infects and destroys erythrocyte precursors resulting in severe anaemia, often requiring multiple blood transfusions.

Many of the drugs used in the management of HIV-positive individuals are myelosuppresive and can both cause and exacerbate anaemia. Most notable is zidovudine, however a review of patients receiving zidovudine in a resource-limited setting in the Democratic Republic of the Congo (previously Zaire), suggested that the presence of baseline anaemia should not preclude the use of zidovudine in resource limited settings as most patients experience improvement of their anaemia in response to the initiation of a zidovudine containing ART regime.[43] This echoed findings by Sullivan *et al.* which showed that zidovudine use was associated with a higher risk of drug-induced anaemia, but was found to be protective against other forms of anaemia.[33] In addition, many of the drugs used in prophylaxis against or treatment of opportunistic infections may cause or aggravate anaemia.[32,44] These include, amongst other, trimethoprim, sulfonamides and several anti-tuberculosis drugs.

The above mentioned conditions mostly affect red cell production, but HIV may also affect red cell survival and destruction. Despite up to a third of HIV-infected patients having a positive direct antiglobulin (Coombs) test (DAT),

clinically significant autoimmune haemolytic anaemia (AIHA) is uncommon.[34] However, there is a real risk of underreporting of the condition due to the difficulty in confirming the diagnosis in the presence of a lack of reticulocytosis, a common finding in HIV-positive patients, i.e. patients may have a low level of AIHA, but due to the fact that, for various reasons associated with their HIV infection, they are unable to mount a reticulocytosis, confirmation of AIHA becomes difficult.[45] In 2008, Olayemi *et al.* screened 98 consecutive HIV-positive patients presenting at their outpatient clinic for routine follow up for AIHA. For the purpose of this study, AIHA was defined as a packed cell volume of less than 30%, a positive DAT and a reticulocyte count of greater than 2.5%.[46] They noted an 11% DAT positivity among their patients with a total of 3% of all of the patients meeting their criteria for AIHA. Anaemia was present in 36.7% of all patient (i.e. Hct <30%) implying that of those who were anaemic, just more than 8% met the criteria for AIHA, suggesting that the condition may not be as rare as what is generally believed. Another cause of HIV-associated red cell destruction is HIV-associated thrombotic thrombocytopenic purpura (TTP). HIV-associated TTP is significantly more common than TTP associated with other conditions.[34,47,48] The association between HIV and TTP was noted during the late 1980's[49,50] and in 2004, Becker *et al.* noted a 0.3% prevalence of thrombotic microangiopathy (TMA) among a group of HIV-positive individuals in the USA and an unadjusted incidence of 0,009 per 100 person-years for TTP.[51] TTP were more common in those with lower CD4 counts and higher viral loads.[51]

HIV-associated TTP is the most frequently encountered TMA in South Africa and is likely a reflection of the extent of the epidemic as well as the, until recently, poor access to ART.[47,48,52,53] It has been postulated that HIV-associated TTP may be triggered through the inflammatory process,[54] which would explain the decreasing incidence after initiation of ART, which also reduces the inflammatory state. Considering then, the relative frequency of both AIHA and TTP in the HIV-positive population, it is essential that clinicians maintain a high index of suspicion for these conditions and actively investigate for their presence wherever doubts exist regarding the etiology of anaemia in HIV.

Early and appropriate diagnosis and investigation of anaemia in HIV is a cardinal point in the management of any person living with HIV. The multifactorial nature of anaemia in HIV can make the investigation thereof a complex and costly exercise, but there are certain basic laboratory investigations which will assist in narrowing the differential diagnosis. Although various publications define anaemia at different haemoglobin (Hb) levels,[55-57] new full blood count reference ranges were published for South Africa in 2009, which suggest the lower limit for Hb in males to be 13,4 g/dL and 11,6 g/dL in females.[58] This is in line with the 1968 WHO report[59] which suggested a patient would be anaemic if the Hb was less than 13 g/dL in adult men and less than 12 g/dL in adult, non-pregnant females.

Determining an accurate Hb level as part of a full blood count (FBC) is therefore the first step in diagnosing and investigating anaemia. Determining the bone marrow response to the anaemia may assist in deciding whether the anaemia is due to a production deficit or due to peripheral loss or destruction and for this a reticulocyte count and reticulocyte production index is helpful. The mean corpuscular volume (MCV) assists in further narrowing the differential diagnosis, with the most common causes of a low MCV being iron deficiency secondary to chronic blood loss. In the setting of HIV, a normal MCV is most commonly associated with ACD and a high MCV with nutritional deficiencies and various drugs. Serum bilirubin levels, serum lactate dehydrogenase and a peripheral blood smear are valuable in assessing cases of suspected peripheral loss or destruction, where AIHA or TTP is suspected. These few simple investigations will assist in delineating the underlying cause of the anaemia in most patients and should ideally be performed prior to the initiation of any therapy, including blood transfusions.

3.2 The impact of antiretroviral therapy

A plethora of articles were published in the 1990's and early parts of the first decade of this millennium on anaemia in HIV, with much of it predating the era of highly active antiretroviral therapy. Today, it is well established that appropriate ART taken regularly, provides long-lasting viral suppression with significant reduction in morbidity and mortality, even though it does not afford a cure and requires lifelong treatment.[14] It has, essentially, converted

what was a uniformly fatal disease, to a chronic, manageable condition for most patients, albeit with a somewhat compromised life-expectancy. Access to ART increased significantly over time, with an estimated 47% of patients in low- and middle income countries who qualify for treatment having access by the end of 2010. In South Africa, an estimated 52-55% of eligible patients had access to ART, meaning that there was still in the region of 1.2 million people eligible for treatment who do not have access.[3,60] It is further estimated that having access to ART resulted in 460 000 (or 30%) fewer South Africans dying from AIDS related causes in 2010 than in 2004[3] and that compared to the 1980's the current life expectancy of a newly infected 20-year old person with access to guideline-recommended therapy at CD4 counts greater than 200/μL is 50.4 years.[61] Johnson et al. (2012)[60] demonstrated in her recently published article, *Access to Antiretroviral Treatment in South Africa, 2004-2011,* that the previously unmet need for ART in South Africa has been reduced by 30% between 2007 and 2011. This was mainly due to the implementation of a comprehensive care, management and treatment program by the South African Department of Health in the latter part of 2003. It was estimated that the adult ART coverage was around 80% by mid-2011, but with major differences between males and females, with more females accessing care than males. This is significantly higher than the 55% coverage reported in the 2011 WHO report and may reflect major uptake during 2010 and the first half of 2011, confirming a major and continued uptake of therapy across South Africa.

Access to ART within in the South African context is likely to have a significant impact on various aspects of health care and health care utilisation as the introduction of ART is associated with fewer hospital admissions and a trend towards shorter lengths of stay, with an overall decrease in health care utilisation once patients have been stabilised on their treatment.[62] It has been clearly demonstrated to reduce health care costs, especially if started early[63-65], and would in all likelihood be cost-effective, even over the associated extended life expectancy of those HIV-infected individual taking appropriate ART.[66] What is less clear is the impact of ART on anaemia and the need for blood transfusions in HIV. Several studies have reviewed the effect of ART on the prevalence of anaemia, with some contradicting results. A recently published study, involving 230 patients from Ethiopia, showed a significant decrease in the prevalence of anaemia after the initiation of ART, but notes that the decrease was not a consistent finding among all those who were commenced on ART.[67] These findings echoed those of the Women's Interagency HIV Study, which showed that ART was associated with resolution of anaemia, even when used for as short as 6 months.[68] This is in contrast to a multi-centre cross-sectional study in the USA in 2007, which showed very little difference in the prevalence of anaemia between those who were receiving ART and those who were not.[69] The fact that this study relied on results from a single visit may have resulted in the confounding findings of the data and requires further investigation. It does, however, echo the

findings of Murphy *et al.* in 2001[70], who found that red blood cell (RBC) transfusion decreased during the course of the Viral Activation Transfusion Study, but that, after adjusting for calendar period and time on the study, the decrease could not be conclusively attributed to the use of ART. From these studies, it is clear that despite the fact that one would expect the prevalence of anaemia and thus the need for transfusion to decrease with access to appropriate ART; this has not yet clearly been established in the literature, with several ambivalent reports being published.

3.3 HIV/AIDS and blood collection

It is interesting to note that the HIV epidemic has irrevocably changed blood collection practices both internationally as well as locally. The emergence and recognition of HIV as a transfusion-transmissible infection, initiated dramatic changes in the collection and testing of donor blood. In many countries, it is this realization of the HIV risk in the blood pool, which resulted in stringent government regulation of blood collection and blood collection centres.[71-74] Similarly, within the South African Blood Services (SANBS) the HIV/AIDS pandemic has had a huge impact on donor recruitment and blood collection.[75] After the initial realization of the threat that HIV holds to the country's blood supply, progressively more stringent donor selection criteria were introduced. New testing technologies were introduced accompanied by the development of a risk model for the release of blood products based on the HIV risk profile of the donor cohort from which it was collected. Many perceived this to be

racial profiling of blood donors and in consultation with the National Department of Health; this risk model was repealed with the introduction of individual donation nucleic acid amplification testing (NAT) to screen for HIV as well as hepatitis B and C.[75] Even today, the very high background prevalence of HIV among the population from which blood donors are recruited, places significant strain on the various blood transfusion services in South Africa.

3.4 HIV/AIDS and blood transfusion

Whereas the impact of HIV on the procurement of blood has been well documented, the specific impact of the epidemic on the utilisation of blood and blood products has not been fully examined, nor is it clear whether there would be a higher prevalence of HIV among patients who require blood transfusions. Considering the high prevalence of HIV among hospitalised patients and the significant risk for anaemia among this group, there would be an expectation that the transfusion requirements of an HIV-infected patient would be higher than that of an HIV-negative patient. We were only able to locate one small study performed at the Groote Schuur Hospital in Cape Town, South Africa, that investigated the impact of HIV on the utilisation of blood products. In reviewing the South African Haemovigilance reports for the period 2007 to 2010, we note a 30% increase in the utilisation of red cell concentrate (RCC) products over this period.[76,77] It is not clear what drove this increase in utilisation but, what is notable, is the analysis in

the 2007 report which indicated that most of the blood issued in the inland provinces of South Africa were issued to medical patients.[76,77] For a country renowned for interpersonal violence and trauma, surgical usage was only about half that of the medical usage. This significant increase in RCC may be due to various reasons, but is likely to include HIV/AIDS.

The Groote Schuur Hospital blood utilisation study aimed to assess HIV as a key driver of the increase in blood and blood products that was identified through the increase in expenditure on blood and blood products in the medical wards of this hospital.[78] They performed a prospective audit to evaluate the impact of HIV/AIDS on blood utilisation. A small cohort of 67 patients who received 590 units of blood and blood products, were identified for inclusion in the study by self-reporting of the prescribing doctors or by the nursing staff who commenced the transfusions. The investigators administered a standardized, structured questionnaire, recording standard demographic data as well as baseline haematological indices, HIV status, CD4 counts and ART regimen (where applicable), reason for admission, co-morbidities, indication for transfusion, number of units transfused and the presence of any transfusion reactions. Of the 67 patients, 61% were HIV-positive and of these, 41% were on ART. Only four of the 17 patients on ART were on an AZT containing regime. Anaemia was the most common indication for transfusion in both the HIV-negative as well as positive groups. However, HIV positivity, especially those not on ART, was associated with significantly

more units of RCC being transfused. Of the 154 RCC transfused, 40 (26%) were issued to HIV-negative patients and 80 (52%) were issued to HIV-positive patients not on ART. Furthermore, of the 397 units of fresh frozen plasma issued, 371 (93%) were issued to HIV-positive patients not on ART, likely reflecting several TTP cases requiring repeated large volume plasma transfusions.

Despite the limited sample size, the voluntary participation of doctors and reliance on self-reporting, these findings are significant and would certainly suggest that in this population, at least, HIV/AIDS is a significant driver of utilisation of blood and blood products and that initiation of ART likely affords protection against conditions requiring the transfusion of blood and blood products, such as chronic anaemia and TTP.[78]

These findings would support the need for further research involving various disciplines and a larger sample size to fully establish the impact of HIV on blood transfusion, in particular, what proportion of blood is transfused to HIV positive patients and whether those who are HIV positive require more blood transfusions than those who are HIV negative. Although there is some suggestion that doctors have been influenced in their prescribing habits by the risk of HIV transmission through blood transfusions, resulting in transfusion at lower Hb levels than before[79], it is unclear whether the prescribing habits of physicians are influenced by a patient's HIV status, i.e.

how rigorously is the cause of the underlying anaemia investigated, is proper informed consent taken and is this application of good transfusion practice[80] dependent on the patient's HIV status?

3.5 Conclusion

In this chapter, we reviewed the pathological relationship between anaemia and HIV and its impact on disease progression and mortality. The need for and benefit of early diagnosis and effective management were reviewed and the potential impact on both blood collection and blood utilization was explored.

The following chapter, Chapter 4, provides a detailed description of the research design and methodologies employed in the study with reference to the various data collection tools. Particular attention is paid to potential causes of errors, bias and confounding and strategies employed to minimize these.

CHAPTER 4: RESEARCH DESIGN AND METHODOLOGY

4.1 Study design

We conducted a cross-sectional study analysing the prevalence of HIV among patients receiving blood and blood products. The study was conducted over a three-month period from 7 January to 7 April 2013.

4.2 Sample selection

Our study population included all patients who were admitted to the Livingstone Hospital in Port Elizabeth during the period 7 January to 7 April 2013. Patients were included through a consecutive enrolment program and represent a convenience sample. Basic demographic and clinical data were collected on all patients admitted to the hospital during this period. Additional detailed data were collected on each patient who received a transfusion of RCC, platelets or fresh frozen plasma (FFP). Patients admitted as in-patients to the applicable wards were included in the study. Although this resulted in a non-randomised study sample, there are no known seasonal variances in blood utilisation among medical and surgical patients and, as the study was expected to run for three months, it covered the admission periods of all the speciality clinics at Livingstone Hospital.

Inclusion criteria:

- All patients admitted as in-patients to the Livingstone Hospital and discharged during the study period.

- All patients receiving blood products, while admitted as in-patients, had a second, detailed data collection form completed.

Exclusion criteria:

- Patients for whom the hospital files could not be located or where critical sections of the files, i.e. sections containing doctors' notes and orders, were missing.
- Where patients had multiple transfusions episodes, those episodes which occurred outside of the study period, were excluded from the data analysis.

4.3 Sample size

Based on the findings of the Groote Schuur Hospital study, we estimated that 52% of blood products would be issued to HIV-positive patients not on ART, 22% to HIV-positive patients on ART and 26% to HIV-negative patients. Using 95% confidence intervals, it was determined that 383 study subjects would be required to confirm a 52% HIV prevalence with ± 5% confidence interval, or 1064 subjects with ± 3% confidence interval among the recipients of blood. If ART and non-treated HIV positive patients are combined, a 74% overall HIV prevalence with ± 5% confidence interval would require 296 subjects while a ± 3% confidence interval would require 821 subjects.

The actual sample consisted of all patients receiving blood and blood products during the period 7 January 2013 to 7 April 2013. Based on historical records from the blood bank which supplies Livingstone Hospital with blood, we expected an average of 450 units of RCC to be issued per month. These units were issued to an estimated 350 patients per month. Using these figures, we anticipated an actual sample size of around 1050 patients receiving 1350 RCC, 544 plasma products and 30 platelet products. Thus we shall have adequate patients to fulfil the sample size estimates given above.

4.4 Measurement

After receiving ethics approval to conduct this study, a formal letter requesting permission to conduct the study at the Livingstone Hospital was sent to the Port Elizabeth Hospital Complex Management. This was followed by a meeting with the appropriate administrative managers, during which a more detailed explanation was provided as to the various aims of the study as well as on the potential operational impact on staff. Upon receiving consent from the Hospital Management to perform the study, additional meetings were arranged with the Heads of the various clinical departments. Information on the study was shared and their cooperation and sanctioning of the study obtained. Thereafter, further meetings were held with the various Interns, Community Service Doctors and Medical Officers to familiarise them with the study.

In the absence of electronic admissions data, Patient Control Sheets (PCS) (Appendix A) were drawn up to log all admissions to the in-patient wards. On the first day of the study, all patients currently admitted to the hospital were logged on the Patient Control Sheets. Each ward had its own sheet allocated. From the second day onward, each ward was visited daily, new admissions logged and discharges recorded. The files of the discharged patients were traced and the basic Discharged Patient Data Form (DPDF) was completed retrospectively for each patient. Each form was allocated a unique barcode number which was specific to a specific admission. The DPDF (Appendix B) was used to capture demographic and basic clinical information for all patients discharged during the study period. This included under which unit and to which ward the patient was admitted, whether the patient was admitted to the Intensive Care Unit (ICU), received a blood transfusion and details with regards to the patient's HIV status. Patients who had more than one distinct admission during the study period had a DPDF completed for each admission and each event was identified with a separate barcode number.

During the study, it was noted that patients were often moved between wards. Certain types of patients were routinely admitted to certain wards but if those wards were full at the time of admission the patient would be transferred to the appropriate ward at a later stage. This resulted in the same patient being recorded in different admission registers with no indication that

the patient was an inter-ward transfer. Furthermore, patients would occasionally receive a "weekend" or "day pass" and may or may not then be readmitted. For the purpose of the study inter-ward transfers and readmissions after a "weekend" or "day pass" were considered as a single admission. However, where patients were clearly discharged and then later admitted, these were considered as two separate admissions, each with its own unique study barcode number. In practice, identifying inter-ward transfers and readmissions after pass-outs were problematic.

In addition, all requests for blood and blood products were identified on a daily basis by reviewing the blood bank records for the preceding 24 hours. All patients who received a blood transfusion were traced and upon discharge, their files traced in a similar fashion as described above. A Transfused Patient Data Form (TPDF) (Appendix C), in addition to the DPDF, was completed for each transfusion episode. Any written or oral request for blood or blood products received by the blood bank was considered a transfusion episode. Where, after full assessment of the patient, additional units was ordered and where it was not initially anticipated that the patient may require additional blood, it was considered an additional transfusion episode. A patient may therefore have more than one transfusion episode in addition to having more than one admission.

Transfusion cases identified from the blood bank had the blood requisition forms for each episode copied and the data transcribed into the applicable fields on the TPDF. Each TPDT had a barcode attached which corresponded with the barcode number allocated to the specific patient on the DPDF which was completed for the corresponding admission during which the transfusion occurred. A new TPFD was completed for each transfusion episode. Where the same patient receives more than one transfusion during the same admission, it was linked by using the same barcode number.

Due to time constraints, the investigator and research assistants were not able to visit each ward every day. Even where wards were visited regularly, it often happened that the files of discharged patients would not be available in the wards. As a result, a significant number of files were not traced in the wards as described above. At the end of the study, the investigators visited the Records Department of the hospital with lists of the files that were outstanding. Repeated efforts were made to trace the files. On occasion, files traced in this manner did not contain any information of the applicable admission, only of the follow-up outpatient visits. In such cases, whatever data were available were collected. Patient records of deceased patients are kept separately and these were reviewed to identify all patients who died during the study period and to trace their files where these were missed in the wards. Figure 3 provides a schematic overview of the data collection process.

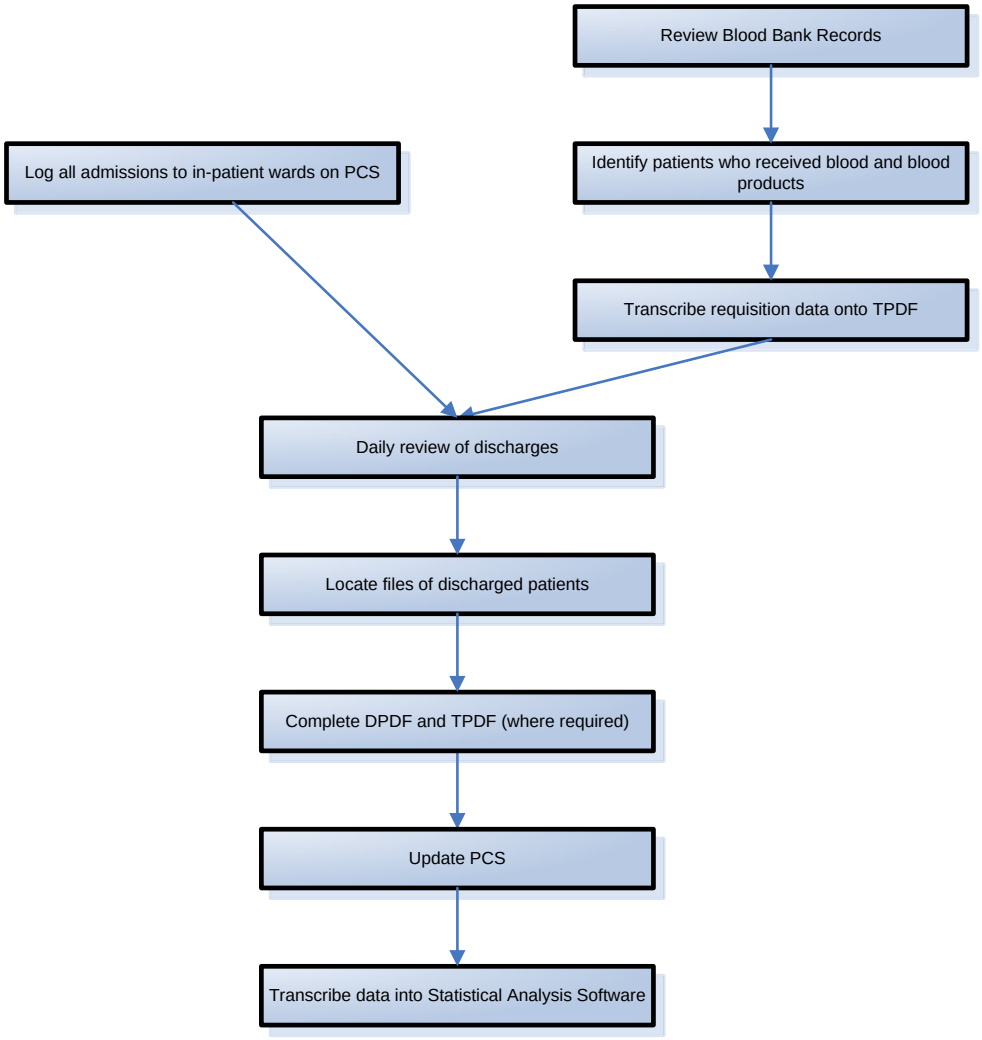


Figure 3: Schematic overview of the data collection process

4.5 Methodological and measurement errors

4.5.1 Random Error (variation)

a) Inter-observer variation

Inter-observer variation was limited through the use of only two additional research assistants other than the main investigator. The intended incumbents are highly experienced, senior blood bank technologists with previous experience in research and data collection.

To aid the observers with the accurate and precise collection and recording of data, all procedures and terminology as well as inclusion and exclusion criteria were clearly defined in advance. Training, including practical "dry-runs", was performed with each of the observers to ensure consistency and precision in the collection, recording and coding of all data. Regular quality assurance checks were performed on the data collection, recording and coding procedures. Weekly meetings were held for the duration of the data collection period where the preceding week's data collection was discussed, problems identified and feedback provided. In addition, the principal investigator reviewed at least 10% of the other investigators' forms to ensure consistency and accuracy in data collection and recording. Any variance was investigated and corrected.

As the study required consecutive patient enrolment, there was a risk of "observer exhaustion" as it required daily trips to the blood bank. However, with the assistance of the additional observers as well as the relatively short data collection period, it was possible for the three observers to manage the data collection. Performing research and clinical audits remains a requirement of the main investigator's position within SANBS and her line manager had provided the approval for her to perform this study as part of her work requirements.

b) Intra-observer variation

Transcribing errors and the deciphering of what may at times be illegible handwriting was one of the biggest potential causes of intra observer variation. The use of only three, highly trained and motivated observers aided in limiting transcription errors and where possible printed laboratory results, either on paper or electronically, were used to limit incorrect deciphering of illegible handwriting. It should be noted that the availability of printed laboratory results were the exception rather than the rule.

4.5.2 Systematic error (bias)

a) Sampling

In certain cases, consecutive sampling lends itself to the introduction of selection bias. Even though this study relied on consecutive sampling, selection bias was unlikely to have occurred. There is no documented seasonality associated with RCC transfusion and as the enrolment period spanned three months, it included the admission periods of all the various specialist clinics at the hospital. January is the month when new interns start working in the hospital and there are anecdotal reports that new interns have a more liberal approach to transfusion but this has not been formally described and did not affect selection as they were probably equally inclined to either over or under transfuse both HIV-positive and negative patients.

There was the possibility of membership bias as only those admitted to hospital were studied and those who are admitted have been shown to have a higher likelihood of being HIV-positive. Similarly, anaemic patients who are HIV-negative may, due to chronic bed shortages as a result of the HIV epidemic, not be admitted and thus be "at risk" of not getting a transfusion. In so far as this may result in more anaemic HIV-positive patients being admitted, it is unlikely to have confounded the results of the current distribution of blood transfusions between HIV-positive and negative patients, but could theoretically misrepresent what the distribution would be, should all patients have equal access to admission. To this end it is essential to detail the nature of the study population so that the findings of the study are not inappropriately translated to other, dissimilar populations.

With the strict policies and procedures in place within the blood banks, we had reliable, accurate records on all patients receiving blood. Of concern is the risk of inaccurate data having been provided to the blood bank in the first place, which could include inaccurate information on admission wards. This may have led to some cases being missed. In addition, some patient files were sent for archiving before the investigators had the opportunity to review their records. Finding these patient files in the Records Department of the hospital was challenging and led to drop-out due to the inability to locate the records of some patients. Review of the mortuary records helped to limit the risk of most of the drop-out being due to patients dying. In order to reduce

drop-out due to the unavailability of records, early, and where possible, immediate follow-up of cases, mostly within 24 hours of discharge was performed. Where dropout does occur, accurate records with detailed reasons for the drop-out were maintained.

Admission rate bias (Berkson's bias) may be of concern. In South Africa, HIV-positive patients mostly fall in to two categories. There are those who present late in the course of the disease, usually severely ill, often requiring admission. And then there are those who are very regularly monitored, probably more so than any other chronically ill population group. This may have result in the anaemia in HIV-positive patients being diagnosed either very late, with late presentation, or very early in the regularly monitored patient. Either way, there is a risk of HIV-positive anaemic patients being admitted more frequently than their negative counterparts, resulting in a possible underrepresentation of similarly anaemic HIV-negative patients, especially among the moderately anaemic groups. Not being admitted reduces the "risk" of transfusion and with the possibility of fewer moderately anaemic HIV-negative patients being admitted, it may incorrectly appear that moderately anaemic HIV-positive patients are at higher risk of being transfused than those who are HIV-negative. However, the main focus of this study was to analyse actual utilisation as well as the availability of information, rather than an extensive analysis on the appropriateness of care.

The latter would require a different study method and is beyond the scope of this investigation.

b) Measurement procedures

Although the collection of data was not blinded, i.e. the observers were aware of the HIV status of the patient; the nature of the data collected was concrete with limited reliance on observer interpretation. As a result, the fact that the observer was aware of both the exposure as well as the outcome, should not materially affect the data collection. Furthermore, the concrete nature of the data being collected greatly assisted in limiting bias.

Exposure suspicion bias is not likely to have played a role in this investigation as both groups had the same outcome and exposure and, in addition, the exposure severity (Hb level) was measured independently by a third party not involved in the study.

However, diagnostic suspicion bias may have been a factor as the investigator, through the course of her normal duties, may influence, for example, the number of units of a particular blood product issued to a patient. Knowing whether or not the patient is HIV-positive may potentially have influenced the investigator to either limit or suggest additional units to be issued where she suspects inappropriate transfusion. To limit the possibility of this occurring, the investigator refrained from vetting or altering

RCC requisitions during the study period, except in cases where the standard of care was clearly substandard and may have led to patient harm. Such intervention, where absolutely required, was applied equally, regardless of the HIV status of the patient. There were no instances during the study period where the investigator was called upon to moderate the transfusion requirements of a particular patient.

In addition, we need to be aware of the potential for ascertainment bias where the quality of information recorded in the medical records by the doctors may have differed between HIV-positive and –negative patients. This is outside of the control of the investigators, but will be recorded and reported if noticed.

c) Execution of study

There is a clear risk of the doctors having changed their prescribing habits as a result of their awareness of the study being conducted, a type of Hawthorne effect, where people perform better due to the knowledge that they are being observed. One way of limiting the effect this may have had on the study, was to fully explain the study and study objectives only to the hospital management and the heads of department, but to blind the actual prescribing doctors as to the exact nature of the research questions, i.e. not detailing that the study is evaluating the prevalence of HIV among the recipients of blood products. In addition, the investigators collected data from

the wards during early mornings and/or late afternoons, when the doctors were less likely to be in the wards.

d) Analysis

Analysis bias is introduced when researchers allow their natural tendency to notice only that which they expect to see or find and to ignore, often unconsciously, those things which are inconsistent with what they expect to find. We mitigated the risk of analysis bias by having an independent party perform the data analysis. In addition, we continuously challenged our assumptions and specifically reviewed the data with a view to identifying unexpected themes and patterns.

e) Interpretation

Data analysis was performed using standard statistical analysis by an independent third party, not involved in the collection of the data. The outcome of the study is being reported regardless of the final outcome. As the investigator aimed to describe current practice, there is no confirmation of hypothesis and thus very limited reason for confirmation bias.

4.5.3 Confounding factors

Several factors may have contributed to the confounding of the findings of this study. These include the age, race, gender and socio-economic status of the study participants. In the HIV-positive group whether or not a patient

receives ART as well as the type of ART regime the patient is on, may lead to confounding. In addition, individual physician practice and preference may also influence the outcome.

It is well-known that HIV has a specific age distribution, occurring most commonly among adults aged 15 to 49 years of age. Age also affects the prevalence of anaemia and thus the need for transfusion, with increasing risk of anaemia with increasing age, the latter being especially true in the HIV-negative population. Black race is not only strongly associated with the prevalence of HIV, but also with anaemia and thus the possible need for transfusion. In South Africa the vast majority of HIV positive patients are black. Black race has also been shown to be an independent predictor of anaemia in HIV-positive patients and thus may lead to significant confounding of the results. There are similar issues with regards to gender. HIV infection is more common among females, specifically those of childbearing age. Furthermore, anaemia is also common in this group, usually due to iron deficiency secondary to menstrual losses and pregnancies. We controlled for the effect of the various demographic factors through analysis and in particular through multivariate logistic regression analysis.

As we did not collect information on socio-economic status, we are not able to use analysis to control for this factor. Low socio-economic status is highly associated with HIV infection and anaemia, the latter usually due to poor

access to healthcare and poor nutritional status. However, we only collected our data from one public sector hospital which serves mainly patients from low socio-economic groups and so there will be a systematic exclusion of mid and high socio-economic groups through the fact that we will only be collecting data from this particular hospital.

As mentioned previously, there is some evidence to suggest that receiving ART influences the prevalence of anaemia among HIV-positive individuals and thus the need for transfusion. ART may, as a result, have significant effect on the outcome of this study. In addition, zidovudine has been shown to cause and/or aggravate anaemia in this population group and can therefore further confound the results. We controlled for this through the collection of data on whether or not patient were on ART and whether or not the ART regime includes zidovudine and included these variables in the analysis.

Individual physician practice and preference may also have influenced the data through the fact that certain physicians may be more likely to be treating HIV-positive patients. In this case, certain specific "firms" – a consultant with his team of doctors and interns – may be responsible for the HIV wellness clinic resulting in most of the HIV admissions to be admitted by a particular group of doctors. If the prevailing transfusion practice among this group is either very liberal or very restrictive, it could have significant bearing on the

outcome. For this reason, we recorded the firm responsible for the patient and included this in our final analysis of the data.

Most doctors will not transfuse terminally ill patients as liberally as those who are for active treatment, usually transfusing at lower Hb levels and with lower Hb targets. Many HIV-positive patients are admitted for palliative care, often dying within a few days of admission. It is, however, not easy to make a simple determination of which patients are for palliative care. We were able to determine whether a patient passed away during a particular admission and included it as part of the overall analysis of the data.

Certain co-morbid conditions, such as tuberculosis, and drugs, such as trimethoprim and sulfonamides, are more common among HIV-positive patients and can either cause or aggravate anaemia. However, collection of co-morbid conditions and prescription of drugs beyond the ART fall outside of the scope of this study and the investigators accept that this may lead to some residual confounding, but we are of the opinion that it will not be significant enough so as to invalidate the outcome.

4.6 Pilot study

A pilot study involving five patients and one day's admissions was performed prior to the commencement of the formal study, but only after the receipt of the required Ethics and Institutional approval. The pilot study was conducted

in the same wards and hospital as the main study. During the pilot study the investigator assessed the logistics that was put in place for the main study. Particular attention was paid to the ease of use of the various data collection forms, the time it took to complete each questionnaire and whether there were any errors or omissions missed in the development phase. Minor amendments were made to the data forms following the pilot study, mostly involving the addition of different clinical firms. Training, including practical "dry-runs", was performed with each of the observers to ensure consistency and precision in the collection, recording and coding of all data.

In addition, we assessed our ability to trace and do the follow-up on the patients as well as the availability and completeness of the patient records. This informed the manner in which the investigators went through the wards to collect the data. No significant changes were made to the study protocol as a result of the pilot study. Data collected during the pilot study were nevertheless not included in the main study.

4.7 Analysis of the data

The data was coded by the Department of Biostatistics of the University of the Free State and analysed by Ms Z Kaidarova from the Blood Systems Research Institute, San Francisco, California, USA. Standard summary statistics were used to characterise the study subjects by age, gender and other demographic data. A primary analysis was performed to compare the

outcome of having received a transfusion between those subjects who are HIV-negative compared to those who are HIV-positive. A secondary analysis looked at the speciality distribution to which the study subjects were admitted and compared the HIV prevalence among the recipients of blood and blood products between the various specialities. Additional analyses considered the number of RCC units transfused, mean and median pre- and post-transfusion HB as well as Hb increments as continuous outcome variables. Multivariable logistic regression modelling was used to assess independent associations with having received a transfusion.

4.8 Implementation of findings

The findings of this research will be presented locally to the management of the Port Elizabeth Hospital Complex, but also to the Provincial Department of Health, and where possible, the National Departments of Health, to inform future budgetary decision making in relation to blood products, but also in relation to the learning and development needs of doctors prescribing blood and blood products. In addition, the findings will be presented to the SANBS and the Western Province Blood Transfusion Service (WPBTS) to assist in the long-term business planning to meet the country's blood needs.

The researcher aims to submit abstracts to appropriate national and international congresses as well as manuscripts for publication in peer-reviewed academic journals so as to raise awareness of the issues identified

and addressed through this research and thereby aiding in the appropriate utilisation of what is a scarce and costly resource.

4.9 Time schedule

It is anticipated that the study will be completed over a 2 year period. Taking critical time points with regards to the submission and approval of the associated protocol and dissertation in to consideration, it is expected that the completed dissertation will be submitted by 31 January 2014 (Table 1).

Table 1: Time schedule for executing research

Develop research questions and timelines and start literature review and methods sections of research protocol.	Mar 2012
Submit Section A of the "Procedure for the Registration of the Title and Nomination of External Examiners" to the Post Graduate Administration Office of the Faculty of Health Sciences for approval by the Executive Committee (EXCO) of the Faculty of Health Sciences.	10 May 2012
Develop literature review, purpose & aim, method and timeline sections of protocol. Develop the outcomes & implementation as well as the budget sections of the protocol	15 May 2012
Executive Committee of the School of Medicine, UFS, meets	29 May 2012
Arrange meeting with the UFS Evaluation Committee	5 Jun. 2012
Complete all outstanding sections of the protocol and submit	23 Jul. 2012

to Chairman of the Evaluation Committee.	
Meet with the Evaluation Committee	30 Jul. 2012
Obtain provisional approval from the Hospital Management	Aug. 2012
Chairman of the Evaluation Committee completes Section B of the "Procedure for the Registration of the Title and Nomination of External Examiners" and submits it to Secretary of the EXCO.	Oct. 2012
EXCO evaluates Title and External Examiners	Oct. 2012
EXCO Secretary submits Title to the Faculty Board	Oct. 2012
Confirm with the Postgraduate Administration Office that the Title, Registration and Appointment of External Examiners had been submitted to the Faculty Board	Oct. 2012
Submit for UFS, SANBS and WSU Ethics Committees	Sep. to Oct. 2012
Faculty Board meets to assess the application	23 Oct. 2012
Study leader completes the "Internal Registration or Amendment of a Title of a Thesis and/or Amendment of Appointment of External Examiners" document as soon as the Faculty Board approves the title and external examiners and submits it to the Postgraduate Administration Office	30 Oct. 2012
Follow-up meeting with Hospital Management, Head of Department for Medicine	Nov. 2012
Collect data	Jan. to Mar. 2013
Clean-up of data, tracing missing records.	Apr. to Aug. 2013

Perform, or have performed, the data interpretation and analysis, commence with writing the literature review and methods sections of the thesis	Aug. to Nov. 2013
Writing up of thesis	Nov. to Dec. 2013
Submit the "Notice of Submission" form to the Post Graduate Administration office prior to 26 October 2013 (for winter graduation 2014)	26 Oct. 2013
Submit thesis by 31 January 2014 if aiming to graduate during the winter graduation of 2014	31 Jan 2014

4.10 Budget

Funding for this Master's degree was obtained from the South African National Blood Services, the employer of the investigator. Any shortfalls were funded utilizing personal funds (Table 2).

Table 2: Estimated budget for executing the study

Budget Item	**Amount**
Student Fees (2012 & 2013)	R25 000-00
Travel Costs (2012 & 2013)	R25 000-00
Stationary	R15 000-00
Professional editing of thesis	R 5 000-00
Total Cost:	**R70 000-00**

4.11 Ethical aspects

This study was performed to the ethical and scientific standards as set out by the ethics committee of the Faculty of Health Sciences of the University of the Free State and in the Research and Ethics policy document of SANBS.

Honesty, integrity and transparency formed the basis for all actions taken during the planning and execution of this study. All stakeholders, including the patients and staff of the hospital as well as those from SANBS were treated with respect, with due deference paid to cultural differences. Where information relevant to a patient's condition became available to the investigators, the information was immediately relayed to the attending doctor. There are no known conflict of interest relating to this study and the investigator. Feedback to the various stakeholders and any scientific publications emanating from this study will be handled in a sensitive yet frank manner.

4.11.1 Ethics approval

The protocol with all supporting documents was submitted to the ethics committee of the Faculty of Health Sciences of the University of the Free State for approval. Approval was also be obtained from the SANBS Human Research and Ethics Committee (HREC), as all research performed by SANBS employees or utilising SANBS data requires approval from its HREC. It is a

requirement that all research performed in the Port Elizabeth Hospital Complex obtain approval from the Eastern Cape Department of Health's Research and Epidemiology Directorate and thus, the protocol and all additional paperwork, were also successfully submitted to this committee.

4.11.2 Institutional approval

The research protocol was submitted to Dr N.N Qangule, the Acting Chief Executive Officer of the Port Elizabeth Hospital Complex, as well as Dr R May, the Medical Superintendent of the Livingstone Hospital for approval and consent to perform the investigation. Furthermore, we obtained the consent of the various heads of departments as well as from the applicable nursing managers for the various departments and wards in which the study was conducted.

In addition, consent to access and use of data from the applicable patients and blood banks was obtained from Dr Loyiso Mpuntsha, the Chief Executive Officer and Dr Charlotte Ingram, the Medical Director, of the SANBS. Similarly, local approval and consent for the study was obtained from the Eastern Cape Zone Technical Manager of SANBS as well as the Blood Bank Supervisor of the local blood bank.

Finally, the local manager of the National Health Laboratory Services (NHLs) who provided pathology laboratory services to the Livingstone hospital was

notified and his/her assistance requested with the location of missing laboratory results.

4.11.3 Confidentiality

Only the investigators had access to personal identifiable data from the study participants. The investigator ensured that all paper records were kept in a locked cabinet and all digital information was kept on a personal computer with strict access control utilising password protection and the required firewalls. There was no breach in confidentiality.

4.11.4 Informed consent

In addition to Ethical Committee Approval, the research protocol was submitted to Dr NN Qangule, the Acting Chief Executive Officer of the Port Elizabeth Hospital Complex as well as Dr R May, the Medical Superintendent of the Livingstone Hospital for approval and consent to perform the investigation. As the study relied on collecting retrospective data, after the discharge of the patients, it was not possible to obtain consent from individual patients.

4.12 Schematic overview of the study

Figure 4 below provides a schematic overview of the study, explaining the key points in the preparation, execution and finalization of the study.

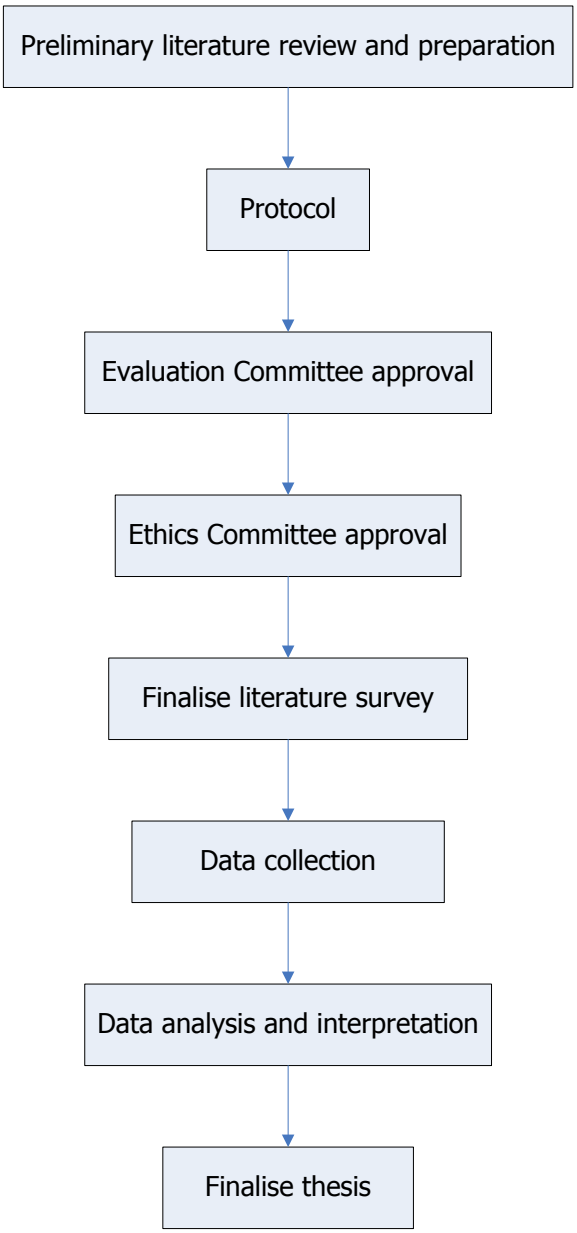


Figure 4: Schematic overview of the study

4.13 Conclusion

In this chapter the research methodology was described in detail, providing a clear description of the methods employed to collect, transcribe and analyse

the data. Ethical considerations were reviewed and a clear schematic overview of the study provided.

The following chapter, Chapter 5, describes the research findings based on the output of the statistical analysis of the data. The data is presented in tables and figures aimed at highlighting the main outcomes of the research.

CHAPTER 5: RESEARCH FINDINGS

5.1 Study Results

A total of 4507 admissions were recorded in the admission registers of the various wards during the time period of the study (Figure 5). Of these, 263 admissions were excluded due to either having been discharged prior to the commencement date of the study (the registers were not kept up to date) or having still been admitted after the closing date of the study. An additional 334 admissions were excluded as duplicate entries. These duplicate entries included patients who were transferred between wards during the same admission or who were given a "pass-out" for a day or two and returned to complete the treatment or investigations for which they were initially admitted. In some cases, these patients were recorded as new admissions and in others they were not formally discharged. For the purpose of this study, these cases were counted as a single admission. There were also a number of cases where an admission was recorded more than once by two different staff members; the duplicate entry was excluded. Finally, there were 3910 admissions which met all the inclusion criteria for the study and of these the investigators were able to trace 3438 patient files, leaving a 12% non-enrollment rate.

Off the 3438 admissions, just fewer than 50% were female (Table 3). The age distribution of the patients suggested a younger patient profile, this despite the fact that the hospital does not have a general paediatric nor

obstetrics and gynaecology department. Just more than 40% of the patient were younger than 40 years and almost three quarters were younger than 60.

Admissions per ward showed that the "medical" wards had the highest number of admissions (41%) followed by the "surgical" wards (38%). In contrast, the medical firms admitted only 36% of the patients and the surgical firms 28%. This is partially explained by the fact that the maxillo-facial department, which makes up the largest proportion of the firms grouped under "Other", generally admitted their patients to the medical wards. Even though Livingstone Hospital does not have a general paediatric ward, it does admit paediatric orthopaedic and surgical cases in a separate ward dedicated for such paediatric patients. Most of the patients admitted to the paediatric ward were orthopaedic cases, explaining the relatively larger case load on the orthopaedic firms as is suggested by the proportion of patients admitted to the adult orthopaedic wards. Around 3% of patients were admitted to the ICU unit at some point during their admission.

HIV status was poorly recorded, with three quarters of patients not having any indication in their files as to what their HIV status may be. About 10% of the patients were reported as being HIV negative and 14% were HIV positive. As expected, the hospital had a very long average length of stay (LOS) with a median LOS of 7 days (mean 11 days). There was no significant difference in LOS between males and females, but with some differences by HIV status.

Patients with an unknown HIV status had a median LOS of 7 days (mean 10 days), while HIV-positive and –negative patients had a mean LOS of 13 (mean 9 days) and 14 (mean 10 days) days, respectively. The overall in-hospital mortality was 8%.

There were 400 patients who received blood transfusions during the study period (Figure 6). Of these, 81 were excluded as the patients received the transfusions in the Trauma Unit and were not admitted as in-patients. A further 52 patients' records were untraceable.

Transfusions occurred in 267 (8%) of the patients, with a similar distribution between male and female patients (Table 4). In contrast to the overall study population, the transfused patients were significantly older (p=<0.0001) (Figure 7), with only 32% of patients younger than 40 years old and only 67% younger than 60. The age groups with the highest proportion of transfusions where 60-69 and >69 year old groups, with 10% and 11% of each group having received transfusions respectively (Table 4).

The surgical wards had the highest number of transfusions with 141 of their 1225 patients being transfused (10%). There were statistically significant differences in the transfusion rates between the various wards (p-value<0.0001). The orthopaedic and medical wards had similar transfusion rates of 6% each. As expected, the lowest transfusion rate was in the

paediatric ward even though these were mostly trauma cases. Even among the various firms, the surgical firms had the highest transfusion rate (12%). Even though the hospital does not have a general paediatric ward, it does admit paediatric surgical and orthopaedic cases. With most of the paediatric admissions being orthopaedic in nature, the overall transfusion rate among all the orthopaedic firms were somewhat lower than that observed among the medical firms, 4% and 7% respectively. The different transfusion rates among the various firms were significant (p-value<0.0001).

Having been admitted to ICU during the course of an admission was associated with a higher transfusion rate (p-value<0.0001) as compared to those patients who were not admitted to ICU during the course of their admissions, with 34% of patients who had been admitted to ICU having received a transfusion. The transfusion rate in ICU was influenced by among other factors, the small number of patients who were "discharged" from ICU. In general, patients were only "discharged" from ICU if they died or required transfer to a specialized ICU at one of the other hospitals in the complex.

Transfusion rates were the lowest among patients with an unknown HIV status (7%) with a no difference in the transfusion rate among HIV-positive and negative patients, 10% respectively. Transfusion rates by HIV status differed significantly within the group (p-value=0.0085). The transfusion rate among HIV-positive patients who were on ART was higher in absolute terms

than those who were not (12% and 8%), but the difference was not significant.

Following the classification of the discharge diagnosis of all the patients, using ICD-10 coding, it was noted that transfusion rates differed across the different diagnostic groupings. The highest transfusion rate was noted among patients with gastro-intestinal haemorrhage (64%), followed by patients were the diagnosis was unknown (13%) and then haematology/oncology patients (11%). These differences were significant (p-value<0.0001).

The overall median LOS among transfused patients was significantly longer than in the non-transfused patients (7 vs. 10 days) (p-value=<0.0001). This pattern was similar among male and female patients; both had significantly longer LOS's among the transfused group. LOS was also longer in the transfused population, regardless of the HIV status, although the LOS among the transfused patients with unknown HIV status (median 8 days; mean 13 days) were shorter than the LOS of those who were HIV-positive (median 12 days; mean 15 days) which in turn were shorter than those who were HIV-negative (median 14 days; mean 24 days). The longer LOS in the transfused patients when compared to those who were not transfused, was statistically significant in the HIV-negative and HIV-unknown group (p-values=0.051 and <0.0001 respectively), but not significant in the HIV-positive group (p-value=0.218). Patients who died in hospital had a significantly higher

transfusion rate (16%) than those who were alive at discharge (7%) (p-value<0.0001).

The above bivariate analyses were performed initially, with calculation of Chi-squared tests and related p-values for associations between each variable and transfusion status. Thereafter logistic regression was performed to calculate unadjusted odds ratios (one predictor variable) and adjusted odds ratios (multiple predictor variable; see Table 4 and 5).

Multivariate logistic regression modelling was performed to control for the various factors which showed significance for transfusion during the bivariate analysis (Table 5). In the final model, patients younger than 18 were significantly less likely to have received a transfusion. However, whereas those aged 70 years or older were significantly more likely to be transfused in the bivariate analysis, this was not true after controlling for sex, firm, ICU admission, alive at discharge, LOS diagnosis. The adjusted odds ratio of transfusion did not differ by sex. HIV-positive patients had an 83% greater odds for having received a transfusion (OR, 1.83; CI, 1.18-2.84) than patients with an unknown HIV status while the odds of receiving a transfusion among HIV-negative patients were not different from the HIV-unknown patients. Among patients admitted by the surgical firms, the odds for transfusion was 2.39 times greater than those admitted by medical firms (OR, 2.39; CI, 1.65-3.47). Patients admission by the orthopaedic and "other" firms were

significantly less like to have received a transfusion (OR, 0.46; CI, 0.23-0.90 and OR, 0.37; CI 0.14-0.97 respectively) Having ever been admitted to ICU (OR, 6.19; CI, 3.61-10.59) was associated with a higher likelihood of having received a transfusion while, in contrast, death at discharge (OR, 1.03; CI, 0.44-2.39) was not. In addition, increasing length of stay was associated with a greater odds ratio of receiving a transfusion. Increasing length of stay demonstrated a "dose-effect", with those patients with a LOS of greater than 14 days having a greater odds (OR, 3.78; CI, 2.46-5.81) than those with a LOS of 6 to 14 days (OR, 1.99; CI, 1.35-2.93) compared to those with a LOS of five or less days. Finally, the selected diagnostic groupings all displayed significant association with having received a transfusion. The biggest odds ratio was noted with GIT haemorrhage (OR, 35.53; CI, 20.07-62.92), followed by patients with an unknown diagnosis (OR, 3.18; CI, 1.45-7.01); trauma patients (OR, 2.89; CI, 1.56-5.22) and patients with haematological or oncological conditions (OR, 1.90; CI, 1.09-3.34).

During 330 transfusion episodes, the 267 transfused patients received 609 units of RBC, i.e. 1.24 transfusion episodes per patient (Table 6). There were no significant differences in the number of transfusion episodes per patient according to HIV status; with 1.18 among HIV-positive patients, 1.19 among HIV-negative patients and 1.26 among patients with an unknown HIV status. In general, there were slightly more units issued than initially ordered with an average of 1.75 units (mean=2) ordered vs. 1.85 units (mean=2) issued per

transfusion episode. This reflects the practice at this hospital of ordering the minimum number of units they think the patient requires and to then phone in for additional units later if the patient's condition suggests additional transfusion is required. The mean number of units ordered per transfusion episode differed between HIV-positive patients (mean=1.57; median=1.00), HIV-negative (mean=1.74; median=2.00) and HIV-unknown (mean=1.80; median 2.00) patients. When comparing the number of units ordered by HIV-status, statistically significantly fewer units were ordered for HIV-positive patients as compared to those with an unknown status (p-value=0.03) while there was no significant difference between HIV-negative and –unknown patients. The same trends were noted with regards to the number of units ordered. Of the 609 units issued, only 6 were not recorded as transfused, giving an issued-to-transfused ratio of 1.00:0.99.

The mean pre-transfusion Hb for all transfusion episodes was 6.71 g/dl (median=6.80 g/dl) with a mean post-transfusion Hb of 8.56 g/dl (median=8.50 g/dl; Figures 8 and 9). The average Hb increment (delta Hb) per transfusion episode was 1.90 g/dl (median=1.70 g/dl). This average increase of 1.90 g/dl is in line with the average of 1.85 units issued per transfusion episode, i.e. ~1 g/dl increase in Hb per unit issued.

The mean pre-transfusion Hb for HIV-positive and –negative patients was significantly lower as compared to those with an unknown HIV-status (p-

values <0.0001 and 0.01 respectively), with a statistically significant lower post-transfusion Hb in the HIV-positive group when compared to the HIV-unknown group (p-value<0.0001). Similar trends were noted when using a T-test to compare the pre-and post-transfusion Hb distributions by HIV-status. There was little difference in the pre-transfusion Hb distribution between HIV-positive and HIV-negative patients or between HIV-negative patients and those with an unknown HIV status and these differences were not statistically significant. However, there was a statistically significant difference between the pre-transfusion Hb distribution in HIV-positive and HIV-unknown patients, with HIV-positive patients having a significantly lower pre-transfusion Hb (p=0.002) (Figure 8). Similarly, HIV-unknown patients had a significantly higher post transfusion Hb distribution as compared to both HIV-positive and –negative patients (p=<0.0001 and 0.005 respectively) with the HIV-unknown patients having been transfused to a higher Hb (Figure 9). The Hb increment per transfusion episode (delta Hb) was lower in the HIV-positive patients, but this difference was not statistically significant. (Figure 10) Analysis of pre- and post-transfusion Hb by firm showed a statistically lower pre- and post-transfusion Hb for the medical firms as compared to both surgical and orthopaedic firms, with no difference between the surgical and orthopaedic firms. The Hb increment per transfusion episode was similar between all three firms (Figures 11, 12 and 13).

Despite 93% of patients having had a FBC prior to the transfusion, only 19% of the patients had further investigations regarding the cause of their anaemia (Table 6). HIV-positive patients were significantly more likely to have had further investigations (38%) than those with an unknown HIV status (13%) (p-value<0.0001) with no significant difference between HIV-positive and HIV-negative patients (24%). In general, the HIV-positive patients had significantly more special investigations done than either those who were HIV-negative or HIV-unknown (Table 6).

Almost all blood requisition forms (97%) were signed by the prescribing doctor with little difference noted according to HIV status. However, 41% of the forms were not signed by the person taking the crossmatch specimen, again with no significant difference noted when looking at HIV status.

Only 69% had consent forms for the transfusion on record. HIV-positive patients had the lowest rate of consent (62%) followed by HIV-unknown (69%) and HIV-negative (76%). These differences were not significant. Of those who did have consent forms on record, 25% was not completed correctly. As with the consent forms, HIV-positive patients had the highest percentage of incorrectly completed forms (49%) and HIV-unknown patients had the lowest (17%). These differences were statistically significant with p-values of <0.0001 for HIV-positive patients and 0.015 for HIV-negative

patients. Only 19 of the 60 HIV-positive associated transfusion episodes had a correctly completed consent form on file (Table 6).

Data was collected on 480 HIV-positive patients of whom 11% were transfused (Table 7). CD4 counts were available on 76% of the patients with a median count of 172 (mean 231). There was a statistically significant difference in the CD4 counts between the transfused and non-transfused HIV-positive patients. Median CD4 count was 67 (mean 164) for the transfused group and 181 (mean 240) for the non-transfused group (t-test, p-value=0.032) (Figure 14). A greater proportion of those on ART were transfused (12%) compared to those who were not on ART (8%). However, those who were on ART prior to the current admission were less likely to be transfused than those who were not on ART (10% vs. 13%) (Table 7).

In total, 57% of the patients on ART were on the recommended first-line regimen of lamivudine/tenofovir/efavirenz, while 6% of patients were on a zidovudine containing regimen and 25% on "other" combinations, mostly regimens containing lamivudine and efavirenz or lamivudine and nevirapine. Data was missing or incomplete in 11% of cases. Although not statistically significant, patients on "other" drug regimens had the highest rate of transfusion (14%), followed by those on a zidovudine containing regimen (13%) followed by those on the standard regimen (8%) (Table 7).

The majority of the HIV positive patients were admitted by the medical firms (60%), followed by the surgical (21%) and then the orthopaedic firms (10%). Within these three specialties, the medical and surgical patients had the highest transfusion rate (11% respectively), followed by the orthopaedic patients (4%). These differences were not significant. Other than the CD4 counts, none of the differences by ART, ART prior to admission, drug regimen or admitting firm were statistically significant (Table 7).

Certain diagnoses were thought to be associated with higher transfusion rates. Patients with a diagnosis of gastro-intestinal haemorrhage had a 17.5 times greater odds of receiving a transfusion as compared to those with a diagnosis of "other" (OR, 17.51; CI, 11.30-27.14). Surprisingly, trauma patients, when compared to patients with an "other" diagnosis did not have a significantly greater odds of transfusion (OR, 1.07; CI, 0.76-1.50), while those for whom the diagnosis were unknown / not recorded did have a significantly greater odds of transfusion (OR, 2.69; CI 1.91-3.78). A diagnosis associated with the so-called diseases of lifestyle (hypertension, diabetes, ischaemic heart disease, stroke and peripheral vascular disease) were noted among 23% of the patients, and these patients had double the odds of transfusion (OR, 2.07; CI, 1.55-2.75) than those who did not (Table 8).

Although not part of the original study question and objectives, a potential association between HIV status and TB or stoke was investigated. The

association between HIV and TB was found to be highly significant (OR, 0.032; CI, 0.02-0.044). Even though the number of cases involving HIV and stroke were fairly small it suggested some association, but this was not significant (OR, 0.63; CI, 0.38-1.07) (Table 9).

5.2 Tables and figures

Table 3: Demographic characteristics of in-patient admissions

Group	Total (N=3438)
Sex:	
Female	1615 (47%)
Male	1804 (53%)
Missing	19 (<1%)
Age:	
0-17	305 (9%)
18-29	582 (17%)
30-39	512 (15%)
40-49	572 (17%)
50-59	560 (16%)
60-69	450 (13%)
>=70	404 (12%)
Missing	53 (1%)
Ward:	
ICU / HI-Care	16 (1%)
Medical	1422 (41%)
Orthopaedics	458 (13%)
Paediatrics	171 (5%)
Surgical	1366 (38%)
Missing	5 (<1%)
Firm:	
ICU	8 (<1%)
Medical	1230 (36%)
Orthopedics	767 (21%)

Group	Total (N=3438)
Surgical	970 (28%)
Missing	214 (6%)
Other	249 (7%)
ICU Admission:	
Yes	97 (3%)
No	3228 (94%)
Missing	113 (3%)
Transfused:	
Yes	267 (8%)
No	3171 (92%)
HIV status:	
Positive	480 (14%)
Negative	327 (10%)
HIV Unknown	2631 (76%)
Alive at discharge:	
Yes	3056 (89%)
No	267 (8%)
Missing	115 (3%)
Length of stay in days:	
	Median (Mean)
Overall	7 (11)
Female	7 (11)
Male	7 (11)
Missing	6 (7)
Positive	9 (13)
Negative	10 (14)
HIV Unknown	7 (10)

Table 4: Characteristics of transfused and non-transfused patients

Group	Non-Transfused 3171 (92%)	Transfused 267 (8%)	P-Value
Sex:			

Group	Non-Transfused 3171 (92%)	Transfused 267 (8%)	P-Value
Female	1487 (92%)	128 (8%)	0.435
Male	1665 (92%)	139 (8%)	
Missing	19 (100%)	0 (0%)	
Age:			
0-17	300 (98%)	5 (2%)	<0.0001
18-29	540 (93%)	42 (7%)	
30-39	474 (93%)	38 (7%)	
40-49	523 (91%)	49 (9%)	
50-59	516 (92%)	44 (8%)	
60-69	406 (90%)	44 (10%)	
>=70	359 (89%)	45 (11%)	
Missing	53 (100%)	0 (0%)	
Ward:			
Medical	1332 (94%)	90 (6%)	<0.0001
ICU / HI-Care	10 (63%)	6 (37%)	
Orthopaedics	431 (94%)	27 (6%)	
Paediatrics	168 (98%)	3 (2%)	
Surgical	1225 (90%)	141 (10%)	
Missing	5 (100%)	0 (0%)	
Firm:			
Medical	1145 (93%)	85 (7%)	<0.0001
ICU	5 (62%)	3 (38%)	
Orthopaedics	733 (96%)	34 (4%)	
Surgical	849 (88%)	121 (12%)	
Other	243 (98%)	6 (2%)	
Missing	196 (92%)	18 (8%)	
ICU Admission:			
No	3004 (93%)	224 (6.94%)	<0.0001
Yes	64 (66%)	33 (34%)	
Missing	103 (91%)	10 (9%)	
HIV status:			
HIV Unknown	2447 (93%)	184 (7%)	0.0085
Positive	429 (90%)	51 (10%)	
On ART: Yes	*253 (88%)*	*35 (12%)*	

Group	Non-Transfused 3171 (92%)	Transfused 267 (8%)	P-Value
No	*165 (92%)*	*14 (8%)*	
Missing	*11 (85%)*	*2 (15%)*	
Negative	295 (90%)	32 (10%)	
Diagnostic Group:			
GIT Haemorrhage	26 (36%)	47 (64%)	
Haematology / Oncology	149 (89%)	19 (11%)	
Trauma	887 (94%)	54 (6%)	<0.0001
Other	1736 (95%)	90 (5%)	
Diagnosis Unknown	373 (87%)	57 (13%)	
Length of stay in days:	Median (Mean)	Median (Mean)	T-test p-value
Overall	7 (10)	10 (15)	<0.0001
Female	7 (10)	10 (16)	0.005
Male	7 (10)	10 (14)	0.002
Missing	6 (7)	0 (0)	
Positive	9 (13)	12 (15)	0.218
Negative	9 (13)	14 (24)	0.051
HIV Unknown	6 (10)	8 (13)	<0.0001
Alive at discharge:			
Yes	2836 (93%)	220 (7%)	
No	223 (84%)	44 (16%)	<0.0001
Missing	112 (97%)	3 (3%)	

Table 5: Multivariable logistic regression analysis of associations with transfusion.

Effect	Unadjusted OR (95% CI)	Adjusted OR (95%CI)
Age:		
0-17	0.21 (0.08-0.55)	0.31 (0.10-0.93)
18-29	1.00 (-)	1.00 (-)
30-39	1.03 (0.65-1.63)	0.93 (0.54-1.60)
40-49	1.20 (0.78-1.85)	1.10 (0.66-1.82)
50-59	1.10 (0.71-1.70)	1.04 (0.61-1.77)

Effect	Unadjusted OR (95% CI)	Adjusted OR (95%CI)
60-69	1.39 (0.90-2.17)	1.41 (0.82-2.44)
>=70	1.61 (1.04-2.51)	1.53 (0.85-2.73)
Sex:		
Female	1.00 (-)	1.00 (-)
Male	1.03 (0.80-1.32)	0.98 (0.73-1.33)
HIV Status:		
HIV Unknown	1.00 (-)	1.00 (-)
HIV Positive	1.58 (1.14-2.19)	1.83 (1.18-2.84)
HIV Negative	1.44 (0.97-2.14)	1.60 (0.98-2.60)
Firm:		
Medical	1.00 (-)	1.00 (-)
ICU	8.08 (1.90-34.38)	1.95 (0.30-12.70)
Orthopaedics	0.63 (0.42-0.94)	0.46 (0.23-0.90)
Other	0.33 (0.14-0.77)	0.37 (0.14-0.97)
Surgical	1.92 (1.44-2.57)	2.39 (1.65-3.47)
ICU Admission:		
No	1.00 (-)	1.00 (-)
Yes	6.192 (4.45-10.75)	6.19 (3.61-10.59)
Alive at Discharge:		
Yes	1.00 (-)	1.00 (-)
No	2.54 (1.79-3.62)	1.03 (0.44-2.39)
Length of Stay:		
<= 5 days	1.00 (-)	1.00 (-)
6-14 days	1.70 (1.24-2.34)	1.99 (1.35-2.93)
>14 days	2.48 (1.78-3.45)	3.78 (2.46-5.81)
Diagnosis:		
Other	1.00 (-)	1.00 (-)
GIT Haemorrhage	34.93 (20.69-58.98)	35.53 (20.07-62.92)
Haematology/Oncology	2.46 (1.46-4.15)	1.90 (1.09-3.34)
Trauma	1.18 (0.83-1.66)	2.89 (1.56-5.22)
Diagnosis Unknown	2.95 (2.08-4.19)	3.18 (1.45-7.01)

Table 6: Transfusion parameters by HIV status for transfusion episodes

		ALL (n=330)	HIV Unknown (232 (70.30%))	HIV+ (60 (18.8%))	P-value	HIV- (38 (11.52%))	P-value
		Mean (Median)	Mean (Median)	Mean (Median)		Mean (Median)	
Transfusion episode/patient		1.24	1.26	1.18		1.19	
Units of RBC Ordered		1.75 (2.00)	1.80 (2.00)	1.57 (1.00)	0.03	1.74 2.00	0.55
Units of RBC Issued		1.85 (2.00)	1.94 (2.00)	1.60 (1.00)	0.01	1.68 2.00	0.08
		N (%)	N (%)	N (%)		N (%)	
Total no. of RBC ordered		572	412 (72)	94 (16)		66 (12)	
Total no. of RBC issued		609	449 (74)	96 (16)		64 (10)	
Units issued, but not transfused	0 Unit	1(17%)	1 (20%)	0 (0%)		0 (0%)	
	1 Unit	5(83%)	4 (80%)	0 (0%)		1 (100%)	
Pre-transfusion Hb		6.71 (6.80)	6.97 (7.00)	5.97 (5.60)	<0.0001	6.30 (6.40)	0.01
Post-transfusion Hb		8.56 (8.50)	8.98 (8.90	7.43 (7.50)	<0.0001	7.77 (8.05)	0.08
Delta Hb		1.90 (1.70)	1.98 (1.70)	1.64 (1.70)	0.22	1.82 (1.75)	0.71
Anaemia investigated:	Yes	62 (19%)	30 (13%)	23 (38%)	<0.0001	9 (24%)	0.11
	No	259 (79%)	193 (83%)	37 (62%)		29 (76%)	
	Missing	9 (3%)	9 (4%)	0 (0%)		0 (0%)	
FBC	Yes	308 (93%)	216 (93%)	57 (95%)	0.49	35 (92%)	0.17
	No	13 (4%)	7 (3%)	3 (5%)		3 (8%)	
	Missing	9 (3%)	9 (4%)	0 (0%)		0 (0%)	
Folate	Yes	37 (11%)	16 (7%)	16 (27%)	<0.0001	5 (13%)	0.22
	No	283 (86%)	207 (90%)	43 (72%)		33 (87%)	
	Missing	10 (3%)	9 (3%)	1 (1%)		0 (0%)	

		ALL (n=330)	HIV Unknown (232 (70.30%))	HIV+ (60 (18.8%))	P-value	HIV- (38 (11.52%))	P-value
B12	Yes	41 (13%)	18 (8%)	15 (25%)	<0.0001	8 (21%)	0.02
	No	278 (84%)	205 (88%)	43 (72%)		30 (79%)	
	Missing	11 (3%)	9 (4%)	2 (3%)		0 (0%)	
Ret Count	Yes	31 (9%)	13 (6%)	12 (20%)	0.001	6 (16%)	0.04
	No	289 (88%)	210 (90%)	47 (78%)		32 (84%)	
	Missing	10 (3%)	9 (4%)	1 (2%)		0 (0%)	
Ferritin	Yes	47 (14%)	22 (9%)	17 (28%)	<0.0001	8 (21%)	0.05
	No	273 (83%)	201 (87%)	42 (70%)		30 (79%)	
	Missing	10 (3%)	9 (4%)	1 (2%)		0 (0%)	
Other	Yes	12 (4%)	6 (3%)	5 (8%)	0.49	1 (3%)	0.99
	No	318 (96%)	226 (97%)	55 (92%)		37 (97%)	
Multiple transfusions	Yes	229 (69%)	163 (70%)	43 (72%)	0.83	23 (61%)	0.23
	No	101 (31%)	69 (30%)	17 (28%)		15 (39%)	
Dr signed for transfusion	Yes	320 (97%)	223 (96%)	60 (100%)		37 (97%)	
	No	6 (2%)	6 (3%)	0 (0%)		0 (0.00%)	
	Missing	4 (1%)	3 (1%)	0 (0%)		1 (3%)	
Signed for taking specimen	Yes	187 (57%)	137 (59%)	30 (50%)	0.15	20 (53%)	0.47
	No	137 (41%)	90 (39%)	30 (50%)		17 (45%)	
	Missing	6 (2%)	5 (2%)	0 (0%)		1 (2%)	
Informed consent in file	Yes	227 (69%)	161 (69%)	37 (62%)	0.12	29 (76%)	0.60
	No	94 (28%)	62 (27%)	23 (38%)		9 (24%)	
	Missing	9 (3%)	9 (4%)	0 (0%)		0 (0%)	

		ALL (n=330)	HIV Unknown (232 (70.30%))	HIV+ (60 (18.8%))	P-value	HIV- (38 (11.52%))	P-value
Consent correctly completed	Yes	165 (73%)	128 (79%)	19 (51%)	<0.0001	18 (62%)	0.02
	No	56 (25%)	27 (17%)	18 (49%)		11 (38%)	
	Missing	6 (2%)	6 (4%)	0 (0%)		0 (0%)	

Table 7: Clinical characteristics of HIV-positive patients

	All (n=480)	Non-transfused (n=429 (89.38%))	Transfused (n=51 (10.63%))	P-value
CD4 Count Available:	N (%)	N (%)	N (%)	
Yes	364 (76%)	323 (89%)	41 (11%)	0.359
No	110 (23%)	101 (92%)	9 (8%)	
Missing	6 (1%)	5 (83%)	1 (17%)	
	Median (Mean)	Median (Mean)	Median (Mean)	T-test p-value
CD4 Count:	172 (232)	181 (240)	67 (164)	0.032
On ART:	N (%)	N (%)	N (%)	
Yes	288 (60%)	253 (88%)	35 (12%)	0.141
No	179 (37%)	165 (92%)	14 (8%)	
Missing	13 (3%)	11 (85%)	2 (15%)	
On ART Prior to Admission:				
Yes	248 (52%)	223 (90%)	25 (10%)	0.331
No	167 (35%)	145 (87%)	22 (13%)	
Missing	65 (14%)	61 (94%)	4 (6%)	
Drug Regimen:				

	All (n=480)	Non-transfused (n=429 (89.38%))	Transfused (n=51 (10.63%))	P-value
Lamivudine/Tenofovir/Efavirenz	142 (57%)	130 (92%)	12 (8%)	
Zidovudine containing regimen	15 (6%)	13 (87%)	2 (13%)	0.532
Other drug combinations	63 (25%)	54 (86%)	9 (14%)	0.208
Missing	28 (11%)	26 (93%)	2 (7%)	
Firm:				
Medical	288 (60%)	256 (89%)	32 (11%)	
Orthopaedics	50 (10%)	48 (96%)	2 (4%)	0.141
Surgical	102 (21%)	91 (89%)	11 (11%)	0.928
Other	12 (3%)	10 (83%)	2 (17%)	0.555
Missing	28 (6%)	24 (86%)	4 (14%)	

Table 8: Transfusion associated diagnoses

	All (n=3438)	Non-transfused (n=3171 (92.2%))	Transfused (n=267 (7.77%))	P-value	OR (95%CI)
GIT Haemorrhage & Trauma	N (%)	N (%)	N (%)		
Other	1962 (57%)	1856 (95%)	106 (5%)	<0.0001	1.00 (-)
PVD / Lower limb amputation	7 (<1%)	7 (100%)	0 (0%)		-
GIT Haemorrhage	100 (3%)	50 (50%)	50 (50%)		17.51 (11.30-27.14)
Trauma	941 (27%)	887 (94%)	54 (6%)		1.07 (0.76-1.50)
Diagnosis Unknown	428 (12%)	371 (87%)	57 (13%)		2.69 (1.91-3.78)
Lifestyle Diseases					
Other	2220 (65%)	2096 (94%)	124 (6%)	<0.0001	1.00 (-)
Lifestyle Diseases	790 (23%)	704 (89%)	86 (11%)		2.07 (1.55-2.75)
Diagnosis Unknown	428 (12%)	371 (87%)	57 (13%)		2.60 (1.86-3.62)

Table 9: HIV associated diagnoses

	HIV+	HIV-	OR (95% CI)
	N (%)	N (%)	
TB+	132 (52%)	91 (3%)	1.00 (-)
TB-	122 (48%)	2665 (97%)	0.032 (0.02-0.044)
Stroke+	17 (7%)	120 (5%)	1.00 (-)
Stroke-	237 (93%)	2363 (95%)	0.63 (0.38-1.07)

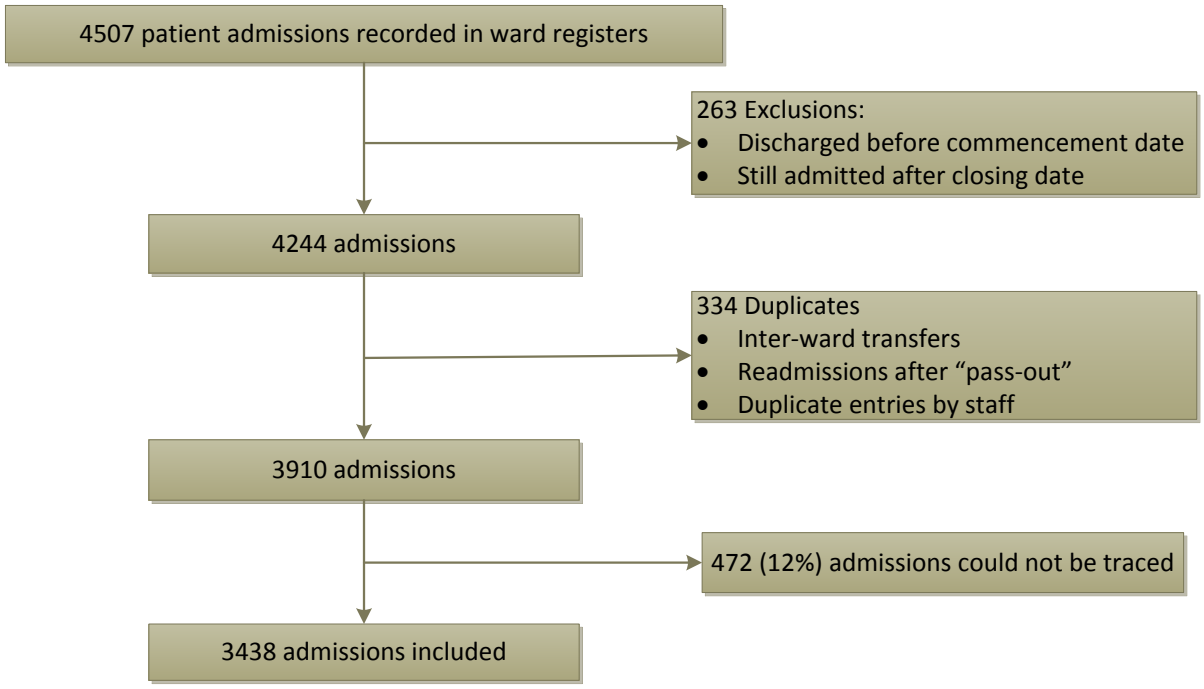


Figure 5: Flowchart showing the inclusion and exclusion of admissions.

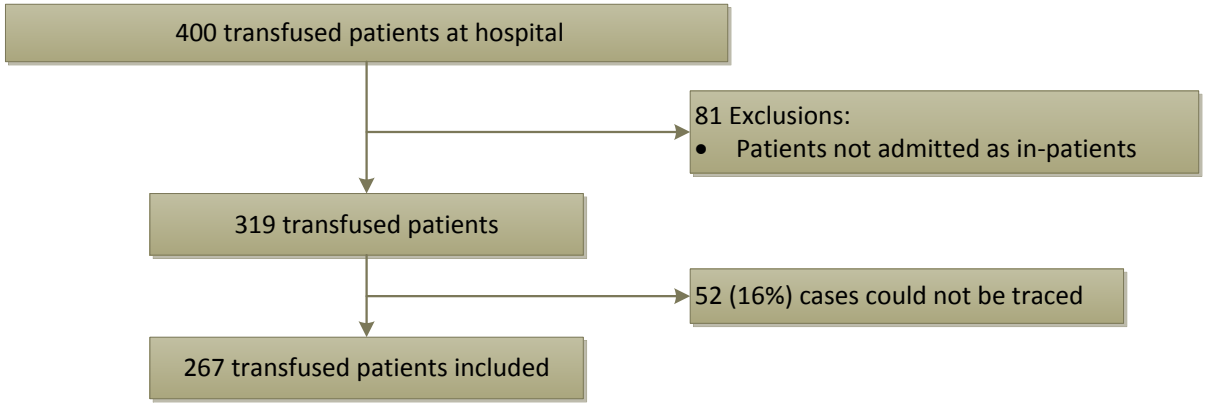


Figure 6: Flowchart showing the inclusion and exclusion of transfused patients.

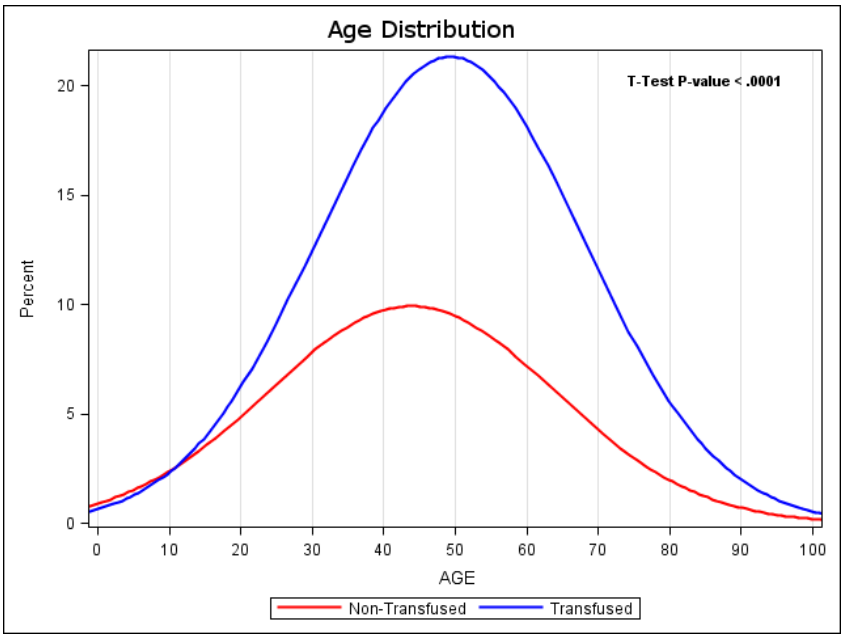


Figure 7: Age distribution by transfusion status.

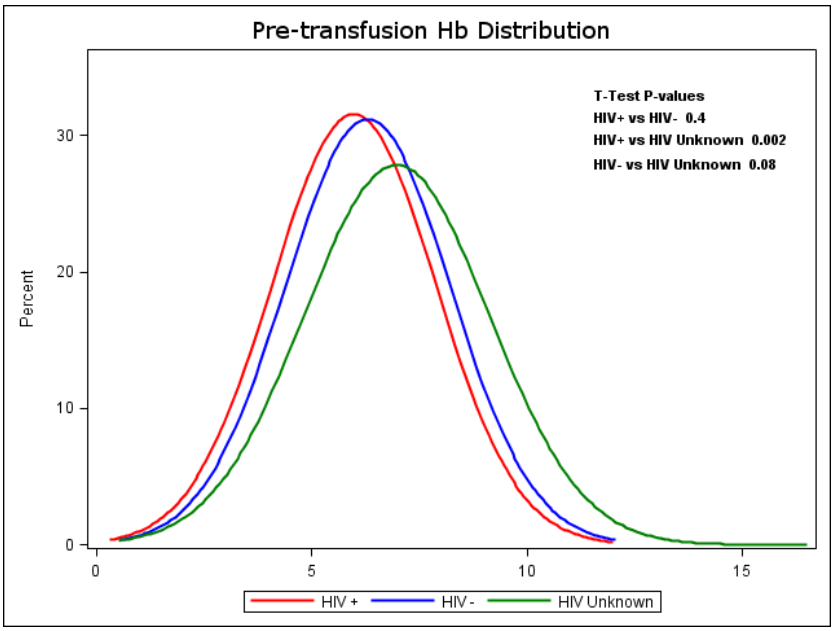


Figure 8: Pre-transfusion Hb distribution by HIV status.

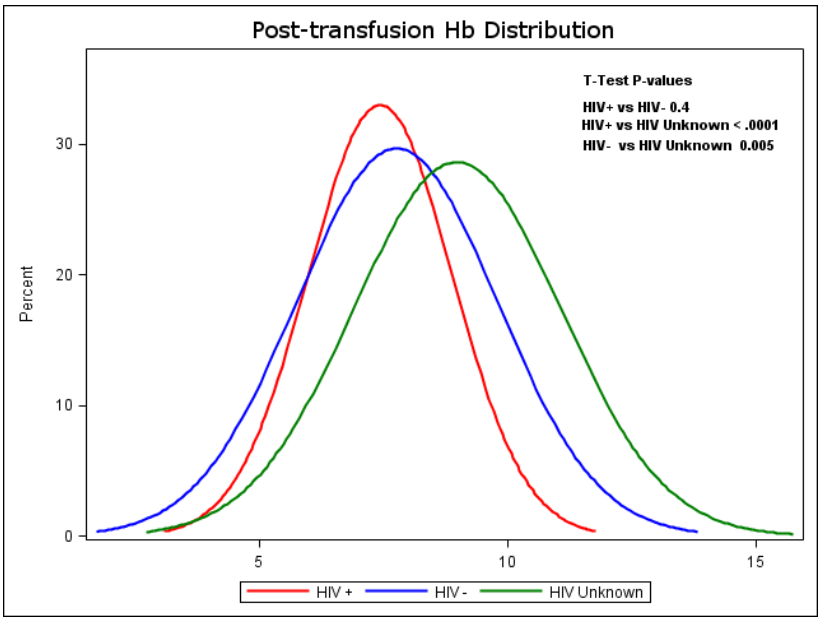


Figure 9: Post-transfusion Hb distribution by HIV status.

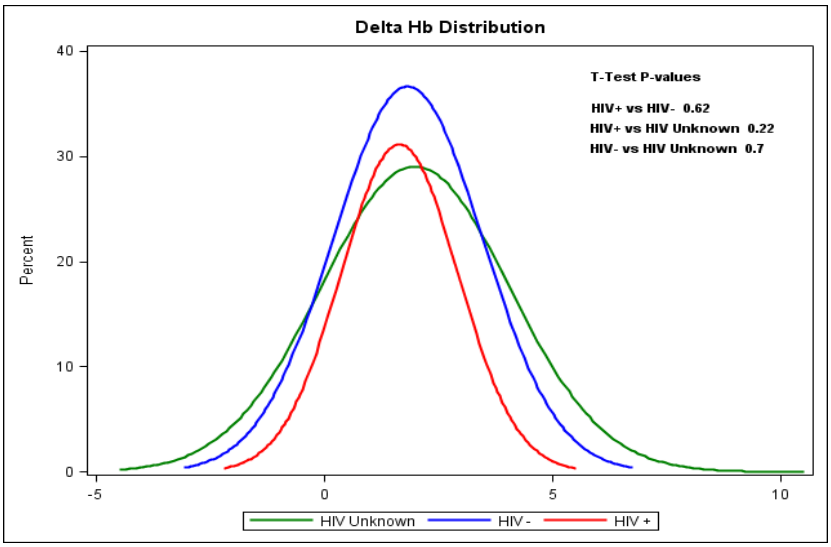


Figure 10: Delta Hb distribution by HIV status.

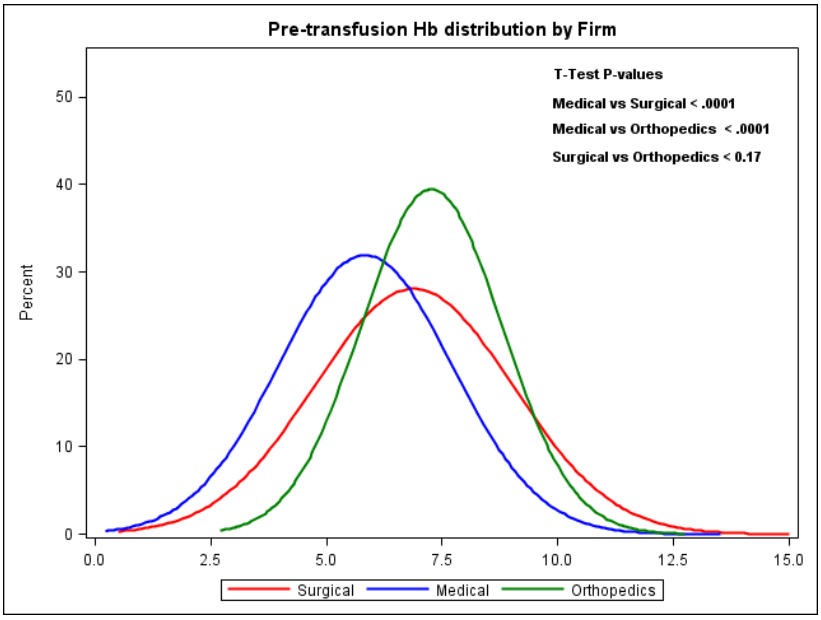


Figure 11: Pre-transfusion Hb distribution by firm

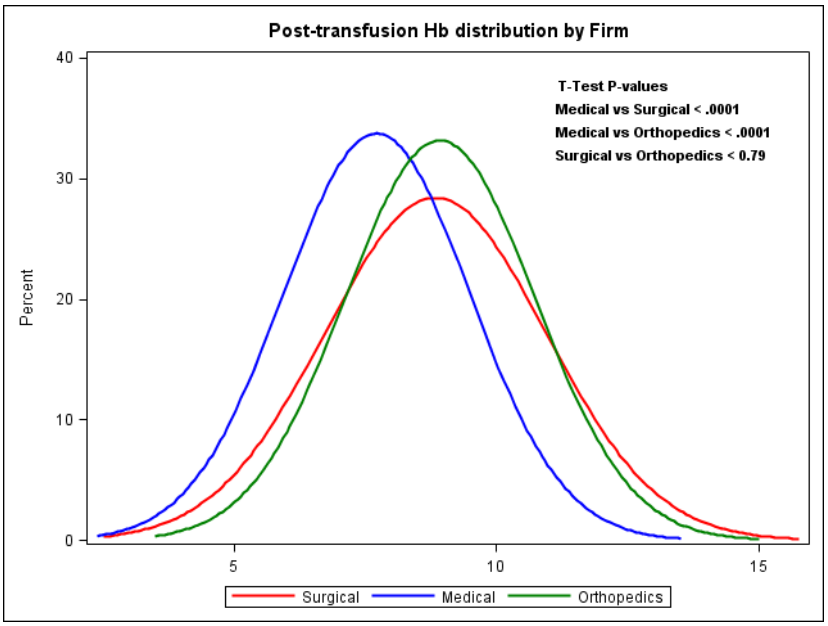


Figure 12: Post-transfusion Hb distribution by firm

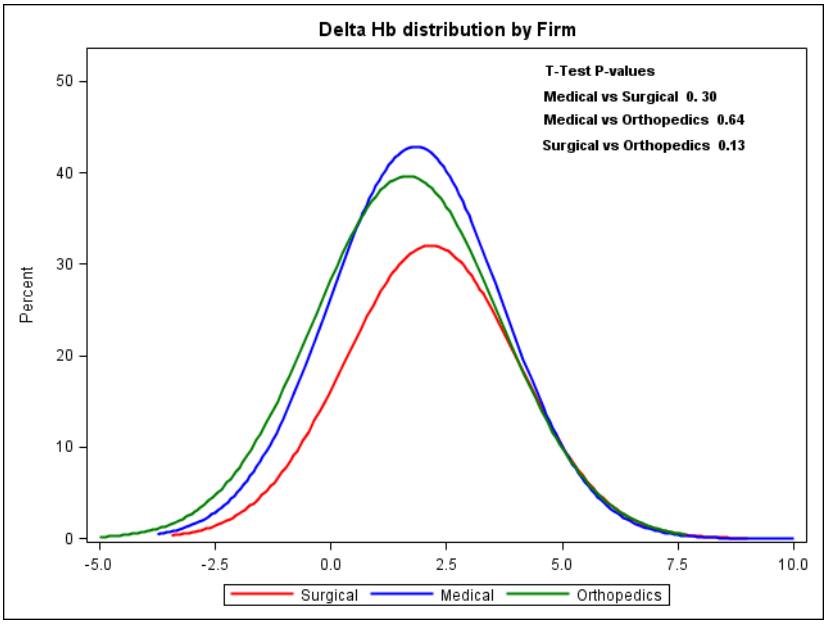


Figure 13: Delta Hb distribution by firm

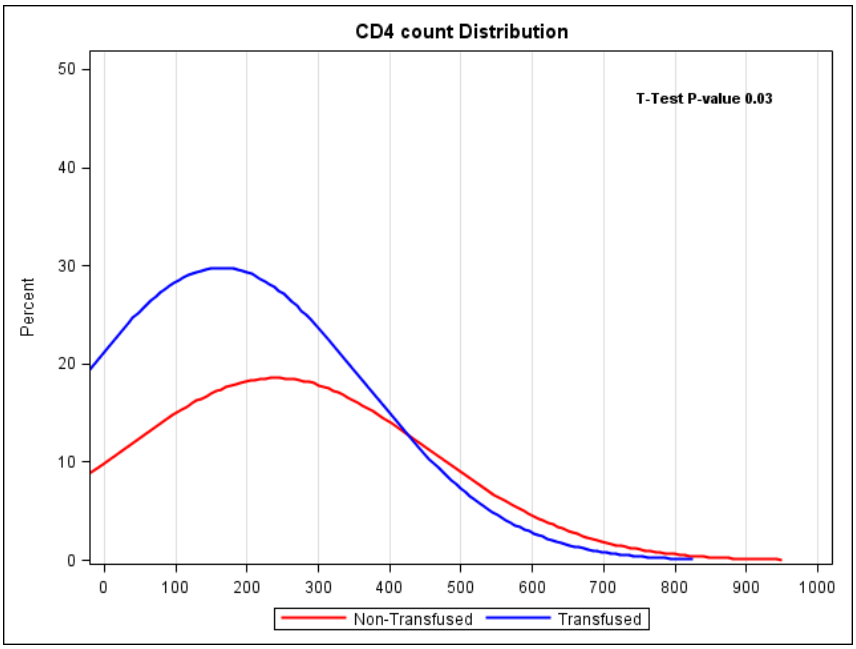


Figure 14: CD4 count distribution by transfusion status

5.3 Conclusion

This chapter reviewed the research findings of the study, using standard summary statistics, bivariate and multivariate analyses. Primary analysis focused on comparing the outcome of having received a transfusion between HIV-positive, -negative and – unknown patients.

The following chapter, chapter 6, focusses on discussing the main findings of the study and placing the results in the appropriate context by further elaborating on the research findings.

CHAPTER 6: DISCUSSION

6.1 Main findings

In this study we set out to determine the impact of HIV on blood utilisation and subsequently the blood need within South Africa as there is very limited information available on how the HIV epidemic may be influencing blood utilisation in the country. The primary aim of the study was to establish the prevalence of HIV among recipients of blood and what proportion of blood is issued to HIV-positive patients. The secondary aim focused on establishing whether HIV influences doctors' prescribing habits in so far as it relates to HIV-positive patients. We further investigated potential associations with transfusion and whether these were influenced by HIV. In addition, we reviewed the current transfusion practices within the hospitals, in particular with regards to pre- and post-transfusion Hb levels, investigation of anaemia and the documentation of informed consent. We were able to analyse the clinical characteristics of the HIV-positive patients and finally, reviewed certain diagnostic associations which became apparent during the data analysis.

The fact that ~75% of patients did not have their HIV status recorded in their files, hampered analysis of the data. Even so, 14% of patients were noted to be HIV-positive and transfusion was significantly increased in these patients. Due to the complex nature of performing HIV testing at this facility, it is likely that HIV is under- rather than over-diagnosed and one should not draw any conclusions based on the reported HIV

prevalence in this study compared to previously published data, suggesting in-patient HIV prevalence rates of between 32 and 54% depending on the discipline being reported on.[22,30,81] Even with the limited information on HIV-status, we were able to demonstrate that almost 20% of the 267 patients who received blood were HIV-positive. The HIV-prevalence among all admissions was found to be ~ 14%, as compared to the almost 20% among the recipients of blood. Similarly 26% of the transfusion episodes involved HIV positive patients. However, only 16% of the units issued were issued to HIV-positive patients. The lack of data on HIV status resulted in an inability to fully assess the potential impact of ART on blood utilisation.

Our study population differed considerably from that of the Groote Schuur Study.[78] The Groote Schuur study had 68.6% females compared to our 47%, had a 61% HIV-prevalence of which 41.5% where on ART as compared to our (recorded) prevalence of 20% with 52% of these patients being on ART prior to admission. However, it would appear that there were some similarities with regards to disease severity, with a median overall CD4 count among our group of 172 and 67 for the transfused patients, compared to the 203 and 74 in the Groote Schuur group.

The Groote Schuur cohort does appear to have had slightly higher mean pre-transfusion Hb levels, 6.1 g/dl for HIV-positive patients not on ART; 7.1 g/dl for HIV-positive patients on ART and 7.3 g/dl for HIV-negative patients compared to our 5.97 g/dl for HIV-positive patients, 6.3 g/dl for HIV-negative patients and 6.97 g/dl for patients with

an unknown HIV-status. Our patients also received fewer units of blood, with a mean number of RBC units transfused of 1.57 for HIV-positive patients compared to the Groote Schuur mean of 3.3 units and 2.0 units respectively for HIV-positive patients not on ART and HIV-positive patient on ART. Post-transfusion Hb levels were not reported in the Groote Schuur study, but the available data would suggest that having higher pre-transfusion Hb levels and receiving more RBC units than our cohort would result in a higher post-transfusion Hb among the Groote Schuur cohort.

Our data suggests that HIV-status significantly influenced doctors' transfusion practices. This is demonstrated by the lower pre- and post-transfusion Hb noted among HIV-positive patients. It would appear that the doctors at this facility had significantly lower transfusion triggers and targets for patients known to be HIV-positive, especially when reviewing our data in relation to the practice reported on in the Groote Schuur study. The pre-transfusion Hb for HIV-positive patients was almost 1 g/dl lower than that of patients with an unknown HIV status (5.97 g/dl vs. 6.97 g/dl). Their post-transfusion Hb was 1.5 g/dl lower than those whose HIV status was unknown (7.43 g/dl vs. 8.98 g/dl). Other potential explanations for this could of course include delayed presentation of patients to medical care, with lower haemoglobins on presentation or a better tolerance of the symptoms of anaemia in a generally younger population. These considerations were not evaluated in this study.

Of concern was the fact that HIV-positive patients were less likely to have had their consent forms completed correctly, with only 61% of the HIV-positive transfused patients having a consent form on file and of those almost half were not completed correctly, resulting in only 32% of these patients having a properly completed consent form on file, as compared to 55% for patients with an unknown HIV status and 47% for HIV-negative patients. Seen together with the significantly lower transfusion triggers and targets, the lack of properly documented consent, raises several legal and ethical issues. In an editorial on the rights of HIV-positive recipient of blood included in a review article on blood and blood products in HIV-positive patients[82], Jonathan Berger commented on restricting access to healthcare based solely on the basis of HIV-status and noted that such actions would be illegal and a breach of the constitutional rights of patients to equality and protection against unfair discrimination.

We were unable to analyse whether the indications for transfusion differed among HIV-positive and –negative patients as this was very infrequently recorded in the patient files. No more than a handful of patients had a clear indication for the transfusion recorded; these included targeting specific Hb levels and in a few cases, symptomatic anaemia. Conversely, HIV-positive patients were more likely to have additional special investigations done, aimed at establishing the underlying causes of the anaemia; this was true across the entire spectrum of special investigations on which data were collected. Whether the more extensive investigations should be attributed to a different

approach by the doctors to HIV and anaemia or whether this was a response to the more severe anaemia in HIV patients is unknown.

At the time, Livingstone Hospital provided mainly medical, surgical and orthopaedic services and although there is no general paediatric services, children requiring surgical or orthopaedic services are admitted to a ward set aside for such paediatric admissions. In addition to these services, it also provides neuro-surgical, maxillofacial and nephrology services, albeit at a much smaller scale. Generally, both the maxillofacial and renal patients are admitted to medical wards, resulting in the medical wards having a mixed case load. This in turn resulted in differing statistics when comparing "wards" and "firms", as the "firms" consisted of a specific work unit usually led by a consultant, registrar/senior medical officer and one or more interns/community service doctors. Thus, when determining the clinical speciality distribution of transfusions, we assessed the differences among the various firms. As expected, the patients admitted by the surgical firms had the greatest odds of transfusion, in fact more than three times greater than medical patients. The surgical patients also had a significantly higher pre- and post-transfusion Hb when compared to their medical counterparts. Pressure from anaesthetists is often cited as the main reason for the more liberal transfusion practices among the surgical firms. However, it is interesting to note that 19% of the transfused patients were transfused for GIT haemorrhage, a condition which rarely required surgical intervention. In addition, the majority of the trauma cases which required transfusion were orthopaedic type injuries, raising questions on the appropriateness of

the transfusion targets within the surgical firms. However, it must be noted that trauma admissions far outnumbered any other diagnostic group, with 887 (26%) of the 3438 admissions being trauma related, suggesting that many of the cases were not associated with significant haemorrhage or that these patients were otherwise young and generally healthy.

Other than the patient's age, the type of admitting firm, being HIV-positive, having been admitted to ICU, having an extended LOS and the primary diagnoses were all variables independently associated with having been transfused. Aside from the surgical cases, the other factors mentioned here, are generally considered to be indicators of disease severity, which would suggest that patients receiving blood transfusions, should be considered at-risk patients and managed accordingly. On the other hand, whether the reverse is true, namely that transfusion may have influenced the length of stay, death or admission to ICU (e.g. waiting for blood, complications of transfusion) cannot be excluded with certainty. Whatever the case may be, it is likely that patients who require transfusion will add a greater degree of pressure on the healthcare services. It is interesting to note that in our model paediatric patients (age <18 years) were less likely to be transfused than young adults (18-29 year-olds), while, contrary to previously published work[83], those older than 69 where found to not have greater odds of transfusion.

With the data we collected, we were able to review the clinical characteristics of the 480 patients who were noted to be HIV positive. Of these, 364 (76%) had a CD4 count recorded with a median CD4 count of 172. As expected, the CD4 counts of the transfused patients were significantly lower, with a median CD4 count among the transfused patients of 67 and 181 among those who were not transfused. This is in line with previously published work which demonstrated increased risk of anaemia with decreasing CD4 counts[36,84], which in turn would increase the risk of requiring a transfusion. Despite the overall low CD4 count, only 60% of the HIV-positive patients were on ART. Of those who required a transfusion, 69% were on ART, but only 49% were on ART prior to admission. Considering the very low CD4 counts among this group, one would have expected a larger proportion of the patients to have already been or to have been started on ART.

After grouping and analysing related diagnoses which appeared to be associated with having had a transfusion, we found that a surprisingly small percentage (6%) of trauma cases required a blood transfusion. Of interest, was the very high transfusion rate (64%) among patients admitted with GIT haemorrhage. Patients with GIT haemorrhage had a more than 35 fold greater odds of transfusion when compared to the rest of the patients. This correlates well with the findings of analyses done on the Kaiser Permanente Northern California database as part of the NHLBI Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) project, which showed 57% of the 15 823 admissions for GIT haemorrhage required RBC transfusions.85 Not surprising was the

high transfusion rates among haematology/oncology patients (11%) and those with disease of the blood or blood forming organs (31%). We also noted a very high transfusion rate among those patients for whom we were unable to find or establish a final diagnosis. Many of these patients had died during the admission with no definitive cause of death noted in the patient files. Death certificates/notifications were not available to us. The high transfusion rate among this group may be explained by the fact that death at discharge was independently associated with receiving a transfusion. In fact, the overall mortality during this period were 8%, but for those who received a transfusion, the mortality rate was 16% and the odds ratio of having received a transfusion was more than twice among patients who died, when compared to those who were alive at discharge.

Though not part of the original objectives of the study, we were able to analyse the relationship between HIV and TB. Not unexpectedly, we noted a very strong association between being HIV-positive and having TB, a clear reflection of the impact of the double epidemic of HIV and TB in South Africa. In fact, 52% of the HIV-positive patients also had TB, a number which correlates very well with previously published work.[22,30,85] Conversely, only 3% of patients with TB were HIV-negative. We were not able to conclusively demonstrate an association between HIV and stroke, but the numbers were small and such an association cannot be excluded.

6.2 Conclusion

In this chapter, the main research findings were discussed and placed into context. Particular emphasis were placed on identifying the differences in blood utilization among HIV-positive and negative patients as well as how HIV-status may influence the prescribing habits of clinicians.

In chapter 7, the main conclusions, limitations and recommendations emanating from the study is highlighted.

CHAPTER 7: CONCLUSIONS, LIMITATIONS AND RECOMMENDATIONS

7.1 Conclusions

The exact prevalence of HIV among recipients of blood remains largely unknown due to the unavailability of the HIV status of the majority of patients admitted to the Livingstone Hospital. However, it is clear that HIV significantly impacts on the need for blood and therefore contributes to the burden on the Blood Transfusion Services to procure sufficient blood to supply in the needs of the country. Furthermore, Blood Transfusion Services should consider the changes in the HIV epidemic when considering the future blood needs of the country. If the trend of diagnosing HIV only late in the disease, as noted at this facility, continues, the burden caused by HIV is likely to continue for the foreseeable future. This is further compounded by the relatively late commencement of ART. Conversely, early diagnosis and early commencement of ART have the potential to alleviate this burden. To this end, it would be strongly recommended that the hospital's complex and logistically challenging HIV-testing policies and protocols urgently be reviewed and measures put in place that will assist in the early and efficient testing of patients, to the point where HIV-testing is offered routinely to patients, rather than only to those where a high index of suspicion exists.

It would appear that HIV-associated anaemia is driving the high transfusion rate among these patients, but there is also the potential that these patients are being

undertreated, even though it would appear that the clinicians more frequently investigate the underlying causes of the anaemia in HIV-positive patients. Whether this practice impacts patient outcome is not clear, and should be further explored, but there is no clear reason why the transfusion needs in chronic anaemia associated with HIV should be managed more restrictively than other causes of chronic anaemia and the reason for this prevailing practice should be further investigated as the data would suggest the potential over transfusion of HIV-negative patients or possible under transfusion of HIV-positive patients. Although an underlying physiological reason for differing transfusion needs cannot be completely excluded.

The lack of information regarding the underlying indication for the transfusion, is a potential medico-legal hazard for the hospital, especially where the need for such a transfusion could be questioned and it will be recommended to the hospital management that this practice be addressed with the clinicians working at the hospital. This may be of particular relevance for the surgical firms who had significantly higher transfusion targets compared to their colleagues and where the routine justification for the practice related to apparent requirements for minimum pre-surgical Hb levels by the anaesthetists. Failure to record that this was the main reason for the transfusion may result in the wrong party having to justify potentially inappropriate clinical practice.

The unexpected finding that HIV-positive patients were significantly less likely to have correctly documented consent for their transfusions is particularly disturbing. In a

country where stigmatisation and discrimination against HIV-positive individuals remains troublesome, this practice is fraught with ethical and medico-legal implications. Not only does failure to obtain informed consent for procedures such as blood transfusion specifically contravene the National Health Act, but to fail to obtain proper consent potentially just because the patient is HIV-positive goes against the very moral fibre of the healthcare profession. One must however, use caution with this information as it is not clear whether the lack of consent for HIV-positive patients may be explained by the fact that most of these patients were medical patients and that surgical patients may routinely be consented for blood transfusion when being consented for surgery.

Many of the conditions associated with receiving a transfusion, are potentially avoidable and include the early diagnosis and effective ART therapy for HIV positive patients, early and aggressive resuscitation of trauma patients and patients with GIT haemorrhage. Non-steroidal anti-inflammatory drug abuse, including over-the-counter preparations such as "Grandpa" (aspirin and paracetamol containing analgesic), is speculated to be one of the leading causes of GIT haemorrhage within patient populations such as that of the Livingstone Hospital. Having an effective prevention strategy aimed at out-patients may potentially not only reduce GIT haemorrhage related admissions, but also decrease the hospital's blood utilisation.

Finally, by multivariable logistic regression modelling, it was demonstrated that patients who receive blood transfusions have a higher morbidity and mortality than those who

did not. This has implications for the general management and nursing of these patients. Doctors and nursing staff alike should be reminded that patients, who receive blood transfusions, are potentially inherently sicker and may require special care and consideration with aggressive management of the underlying disease and active observation for complications, both those associated with transfusion as well as of the underlying disease or condition. Various publications have attempted to assess the association between blood transfusion and morbidity and mortality.[86] Such studies are fraught with difficulty as the mere fact that a patient requires a blood transfusion, suggests severe disease or injury as compared to those who do not require transfusion, leading to indication bias.[87] However, a recent publication by Wu *et al*, found that for every 10% increase in the rate of intraoperative blood transfusion, there was a 0.7% (95% CI: 0.3%-1.1%) decrease in the adjusted 30-day postoperative mortality for high-risk patients.[88] This echoes the findings of a study on morbidity and mortality of blood transfusion in paediatric cardiac surgery.[89] To date, no causal relationship between (appropriate) blood transfusion and mortality has been proven, however, it is clear that patient requiring transfusion should be considered high risk-patients and managed accordingly.

7.2 Limitations

Some of the findings of this study are not generalizable due to the following limitations:

- Livingstone Hospital forms part of Port Elizabeth Hospital Complex which consists of three different hospitals in three different locations throughout the city. Certain specialised disciplines are limited to specific hospitals. In particular, Livingstone Hospital covers mainly three disciplines, namely surgery, internal medicine and orthopaedics. The hospital does not provide any obstetric and gynaecological services, a discipline known for significant blood utilisation as well as a high HIV disease burden.
- In addition, Livingstone Hospital is a tertiary/referral hospital and the patient demographics and disease burden does not necessarily reflect those of the broader patient population of the Eastern Cape Province.
- Clinical information was collected retrospectively utilising the paper-based record system in use at the hospital. This process was plagued by lost patient files, missing documentation, illegible hand-writing and perfunctory note-keeping. Test results were not always recorded in the patients' folders. Despite this, the investigator was able to access almost 90% of the patients' files.
- The lack of HIV status in the vast majority of patient folders was unexpected. During the data collection process it became clear that the current policies and procedures regarding the testing of patients created significant barriers in getting patients tested. It is required that patients receive both pre-and post-test counselling in a confidential environment, administered by speciality trained (and appointed) staff. The lack of confidentiality around the patient's bedside and the lack of a suitable area within a ward results in patients having to be taken out of

the wards to be counselled and tested in a separate area. There is a limited number of staff available to perform this testing. The net result is that many patients are admitted and discharged without being tested, even though HIV-testing was requested by the attending doctors.

- HIV-testing at the hospital is performed with HIV-rapid test kits as an initial screening test. There is some doubt about the sensitivity and specificity of these tests, which are highly user-dependent. In addition, patients appeared to be referred for testing only once their clinical picture is suggestive of HIV/AIDS, implying that several patients with early disease is unlikely to be diagnosed while in hospital – a serious missed opportunity. In the surgical wards the observed practice did not include referring patients for HIV testing and most of the HIV-positive surgical patients had been diagnosed prior to their current admission.
- Other than for a handful of patients, viral loads were not performed at all. On the other hand, CD4 counts were often requested (but only in the medical departments), but often the results were not available by the time the patient was discharged.
- The doctors in this hospital are not in the habit of recording the underlying indication for the transfusion, other than just the Hb. This results in an inability to compare the indication for transfusion across different patient populations.
- There is limited published information on blood utilisation among HIV-positive patients, which limits comparing the findings of this study to the findings of other, similar studies.

7.3 Recommendations

The main recommendations from this study for the Livingstone Hospital are:

- Review the current HIV-testing policies and protocols with the aim of significantly improving the capacity and the logistics for in-patient HIV testing.
- Review the transfusion guidelines, policies and practice, especially among the surgical firms, but also in the apparent discriminant application of transfusion practices involving HIV-positive patients.
- As a matter of some urgency address the overall low rate of consent among transfusion recipients, but with specific emphasis on the need to ensure that proper informed consent is obtained and documented regardless of HIV-status.
- Develop policies and systems aimed at the early diagnosis and management of chronic anaemia in general, but in particular in HIV-positive patients. The causes of anaemia is most often highly treatable and early management is likely to avoid transfusion altogether. Similarly, the early and aggressive management of avoidable factors associated with GIT haemorrhage should be pursued.
- Not only did the inability to trace patient files and missing or incomplete notes hampered data collection for this study, but poses a serious medico-

legal risk for the hospital. Anecdotal reports from various sources within in the Eastern Cape DoH suggest that the Department is often obliged to settle litigation purely because the patient's records are not traceable. In addition, the loss of patient files hampers continuity of care and leads to the unnecessary repetition of tests and investigations, adding to the financial burden on the hospital. Clearly, an effective patient record system will go a long way towards alleviating these problems.

In addition, the following recommendations will be made to the Blood Transfusion Service:

- Changes in the HIV epidemic not only affect potential blood donors, but have a significant impact on the blood requirements of the country and any such changes should be noted and actively investigated when determining the potential blood needs and therefore the blood collection targets for the country.
- Despite the findings of this study, the exact nature of the impact of HIV and the subsequent introduction of ART on the blood utilisation of the country have still not been fully appreciated, and the Blood Services should actively pursue or at least support further research on this topic.

Finally, the following areas for potential future research have been identified:

- Further studies to better understand the significantly lower transfusion targets noted among HIV-positive patients, in particular to assess whether this is the result in differing approaches between HIV-positive and -negative patients or whether there is a physiological reason for HIV-positive patients to tolerate lower Hb levels.
- Evaluation of the apparent greater degree of investigations into the underlying causes of the anaemia associated with HIV as compared to other conditions, specifically to assess whether HIV-positive patients are better evaluated or whether this may in some way be related to the fact that they also have lower pre-and post-transfusion Hb levels, which may suggest that they present with more severe anaemia, therefore prompting more extensive investigation.
- The apparent differing practices with regards to obtaining inform consent warrants further investigation so as to be better equipped to deal with this matter conclusively.
- Finally, studies to identify preventable causes of anaemia leading to the need for blood transfusion, whether acute such as GIT haemorrhage or chronic such as anaemia associated with HIV, may assist on reducing the admission and intervention burden on the hospital, but may also contribute to decreased blood utilisation.

7.4 Concluding remarks

Being able to quantify the impact of the HIV-epidemic on blood utilization will assist in the planning and management of the national and local blood supply and with resource allocation at a provincial and local level. It is hoped that this research will add to the understanding of the impact of HIV on blood utilization, for it is clear that HIV/AIDS does indeed influence blood utilization as well as doctors' prescribing habits.

The study has answered some questions in relation to this topic, but several more remain unanswered and in fact, new questions may have been asked following some of the findings of this research, most important being the potential impact of the massive ART roll-out on future blood utilization. In October 2006, Dr Mangosuthu Buthelezi made the statement: "It is clear before God and man that the entire war on HIV and AIDS has not been waged with any degree of piety, responsibility and care." This researcher is of the opinion that this may potentially still be true today, with HIV-positive patients seemingly being afforded less due care in terms of issues such as informed consent, access to early diagnosis and management and the same consideration of their transfusion needs as those who are HIV-negative.

This being said, the findings of this study are already raising questions at the Livingstone Hospital regarding their transfusion practices and systems to address problems identified through this study are being developed. It is the hope of the

researcher that communicating the findings to a broader audience will influence transfusion practices positively and improve the quality of care patients receive.

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APPENDICES

Appendix A: Patient control sheet

Appendix B: Discharged patient data form

Appendix C: Transfused patient data form

Appendix D: Draft letter of request to the CEO of the Port Elizabeth Hospital Complex

Appendix E: Draft letter of request to the Medical Supervisor of the Livingstone Hospital

Appendix F: Draft letter of request to the Heads of Department at the Livingstone Hospital

Appendix G: Draft Letter of request to the Unit Managers at the Livingstone Hospital

Appendix H: Draft letter of request to the Medical Director and CEO of the South African National Blood Services

Appendix I: Draft letter of request to the Zone Technical Manager of the South African National Blood Services

Appendix J: Draft letter of request to the Blood Bank Supervisor of the Livingstone Blood Bank

Appendix K: Draft letter of request to the Manager of the National Health Laboratory Services

Appendix A – Patient control sheet

Surname	Name	Hos No.	Adm Date	Internal Ward Transfer?	Barcode	Transfused?	No of Transfusions?	D/C Date	D/C Form Completed?

Appendix B – Discharged patient data form

BARCODE: | | | | | | | | |

1-8

DISCHARGED PATIENT DATA FORM

DISCHARGED PATIENT REGISTER DATA	
Demographics	**Office Use:**
Date admitted? (dd/mm/yyyy) ...../...../.....	d d m m y y y y 9-16
Date discharged? (dd/mm/yyyy) ...../...../.....	d d m m y y y y 17 - 24
Patient admitted previously during study period? 0 Yes 1 No	25
Gender: 0 Female 1 Male	26
Age in years: ..... (0-12 months = 1year)	27-28
Ward: 0 ICU / HI-Care; 1 1A; 2 1B; 3 2A; 4 2B; 5 3A; 6 3B; 7 4A; 8 4B; 9 5A; 10 5B; 11 P3	29-30
Admitting firm:	

0	Medical 1	7	Surgical Green	14	Maxillo-Facial
1	Medical 2	8	Surgical Yellow	15	ENT
2	Medical 3	9	Surgical Blue	16	Ophthalmology
3	Ortho A	10	Surgical Platinum	17	ICU
4	Ortho B	11	Surgical ASU	18	Medical 4
5	Ortho C	12	Paed Surgery	19	Club foot clinic
6	Surgical Red	13	Neurosurgery	20	

31-32

Patient admitted to ICU / Hi-Care during this admission?

0	Yes
1	No
2	Unknown

33

Clinical Information	**Office Use:**

Patient transfused during study period?

0	Yes
1	No

34

If yes, Transfused Patient Data Form completed?

0	Yes
1	No

35

HIV Status Recorded

0	Yes
1	No

36

What?

0	Positive
1	Negative
2	Indeterminate

37

If HIV+, is CD4 available?

0	Yes

38

1 No	
If CD4 is available, what is it? ……	☐☐☐ 39-41
If HIV+, is the Viral Load available? 0 Yes 1 No	☐ 42
If Viral Load is available, what is it? ……	☐☐☐☐☐☐ 43-48
If HIV+, is pt on ART? 0 Yes 1 No	☐ 49
If on ART, was pt on ART prior to current admission? 0 Yes 1 No	☐ 50
If on ART, list drugs: …… …… …… 0 AZT – Zidovudine; 1 ddI – Didanosine; 2 3TC – Lamivudine; 3 D4T – Stavudine; 4 ABC – Abacavir; 5 TDF – Tenofovir; 6 FTC - Emtricitabine 7 NVP – Nevirapine; 8 EFV – Efavirenz; 9 ETV - Etravirine; 10 ATV – Atazanavir; 11 LPV/r – Lopinavir/Ritonavir; 12 RAL - Raltegravir; 13 SQV - Saquinavir 14 IDV - Indinavir; 15 Tenofovir; 16 Unknown; 17; 18; 19; 20	☐☐ ☐☐ ☐☐ 51-56
Final Dx available? 0 Yes	☐ 57

1 No	
What was it? …… …… ……. 0 | 7 | 14 1 | 8 | 15 2 | 9 | 16 3 | 10 | 17 4 | 11 | 18 5 | 12 | 19 6 | 13 | 20	☐☐ ☐☐ ☐☐ 58-63
Patient alive at discharge? 0 Yes 1 No	☐ 64
Comments: ……. ……. ……	

Appendix C – Transfused patient data form

BARCODE: | | | | | | | | |

1-8

TRANSFUSED PATIENT DATA FORM

BLOOD REQUISITION FORM DATA	
Demographics	**Office Use:**
Gender: 0 Female 1 Male	9
Age in years: ..... (0-12months = 1year)	10-12
Date Transfusion Request Received: (dd/mm/yyyy) ...../...../.....	d d m m y y y y 13-20
Ward: 0 ICU / HI-Care; 1 1A; 2 1B; 3 2A; 4 2B; 5 3A; 6 3B; 7 4A; 8 4B; 9 5A; 10 5B; 11 P3	21-22
Products Ordered:	**Office Use:**
RCC: No of Units:	23-24
Platelets: No of Units:	25-26
FFPs: No of Units:	27-29

Cryo-poor FFP: No of Units: **……**	30-32
Cryoprecipitate: No of Units: **……**	33-35
Initial type of X-match requested: 0 None 1 Emergency 2 Standard 3 Type & Screen 4 Not applicable	36
Products Issued:	**Office Use:**
RCC: No of Units: ……	37-38
Platelets: : No of Units: ……	39-40
FFPs: : No of Units: ……	41-42
Cryo-poor FFP: No of Units: **……**	43-44
Cryoprecipitate: No of Units: **……**	45-46
Diagnosis / Pregnancies / Transfusions / Discipline	**Office Use:**
Dx provided: 0 Yes 1 No	47
What: ……	

…… …… 0 | 7 | 14 1 | 8 | 15 2 | 9 | 16 3 | 10 | 17 4 | 11 | 18 5 | 12 | 19 6 | 13 | 20	☐☐ ☐☐ ☐☐ 48-53
Hb provided? 0 Yes 1 No	☐ 54
What was the Hb? **……g/dL**	☐☐☐☐ 55-58
HIV status provided: 0 Yes 1 No	☐ 59
Previous pregnancy provided: 0 Yes 1 No 2 Not applicable (Males, girls ≤12 yrs)	☐ 60
Previous transfusion info provided: 0 Yes 1 No	☐ 61
Discipline provided: 0 Yes 1 No	☐ 62

Which:

0	ICU	6	Paediatrics
1	Trauma	7	Medical
2	Gen Surgery	8	Haemo / Oncology
3	Cardio-Thoracic	9	Gynae & Obstets
4	Orthopedics	10	Other
5	Paed Surgery	11	Infectious Complications

63-64

Prescription & Prescriber Info:	**Office Use:**

Dr signed for Tx?

0	Yes
1	No

65

Prescriber contact no provided?

0	Yes
1	No

66

Signed for taking speci?

0	Yes
1	No

67

Time speci taken recorded?

0	Yes
1	No

68

Time requisition received?

.....

h h : m m

69-73

Products ordered for a specific time?

0	Yes
1	No

74

If yes, for what time?

.....

h h : m m

75-79

Time first product collected? ……	☐☐☐☐☐ h h : m m 1-5
Was products cancelled 0 Yes 1 No	☐ 6
Comments: …… ……	

PATIENT FILE DATA

Pre-transfusion Information	**Office Use:**
Date of admission: (dd/mm/yyyy) ……/……/……	☐☐☐☐☐☐☐☐ d d m m y y y y 7-14
Date of discharge: (dd/mm/yyyy) ……/……/……	☐☐☐☐☐☐☐☐ d d m m y y y y 15-22
Treating firm: 0 Medical 1 | 7 Surgical Green | 14 Maxillo-Facial 1 Medical 2 | 8 Surgical Yellow | 15 ENT 2 Medical 3 | 9 Surgical Blue | 16 Ophthalmology 3 Ortho A | 10 Surgical Platinum | 17 ICU 4 Ortho B | 11 Surgical ASU | 18 Medical 4 5 Ortho C | 12 Paed Surgery | 19 Club foot clinic 6 Surgical Red | 13 Neurosurgery | 20	☐☐ 23-24
Dr's script for Tx in file? 0 Yes 1 No	☐ 25

Indication for Tx recorded?

0	Yes
1	No

26

What?

……

……

……

……

0	Symptomatic Anaemia	7		14	
1	Target Hb ≥ 10g/dl	8		15	
2	Target Hb ≥ 8g/dl	9		16	
3	Raised INR	10		17	
4	Active Haemorrhage	11		18	
5		12		19	
6		13		20	

27-32

PreTx Hb?

0	Yes
1	No

33

What was the pre-transfusion Hb?

……..g/dL

34-37

Anaemia invest. bloods taken?

0	Yes
1	No

38

FBC:

0	Yes
1	No

39

Folate:

0	Yes

40

1 No	
B12: 0 Yes 1 No	41
Ret Count: 0 Yes 1 No	42
Ferritin: 0 Yes 1 No	43
Other: …… …… 0 INR 3 RPI 6 1 Bone Marrow 4 Haemolysis Screen 7 2 DIC Screen 5 Other 8	44
Hx of prev. Tx recorded? 0 Yes 1 No	45
HIV Status Recorded? 0 Yes 1 No	46
If yes, what is it? 0 Negative 1 Positive 2 Indeterminate	47
If HIV+, is CD4 available?	

0	Yes
1	No

48

If CD4 is available, what is it?

……

49-51

If HIV+, is the Viral Load available?

0	Yes
1	No

52

If Viral Load is available, what is it?

……

53-58

If HIV+, is pt on ART?

0	Yes
1	No

59

If on ART, was pt on ART prior to current admission?

0	Yes
1	No
2	Unknown

60

If on ART, list drugs:

……

……

……

0	AZT – Zidovudine	7	NVP – Nevirapine	14	IDV - Indinavir
1	ddI – Didanosine	8	EFV – Efavirenz	15	Tenofovir
2	3TC – Lamivudine	9	ETV - Etravirine	16	Unknown
3	D4T – Stavudine	10	ATV – Atazanavir	17	
4	ABC – Abacavir	11	LPV/r – Lopinavir/Ritonavir	18	

61-66

5	TDF – Tenofovir	12	RAL - Raltegravir	19	
6	FTC - Emtricitabine	13	SQV - Saquinavir	20	

1st Tx this admission?

0	Yes
1	No

67

Informed consent in file?

0	Yes
1	No

68

Correctly completed?

0	Yes
1	No

69

Post-Transfusion Information:	**Office use:**
Were all issued units transfused? 0 Yes 1 No	70
If not, how many were NOT Tx? (Number) ……	71
Post Tx Hb done? 0 Yes 1 No	72
What was the post transfusion Hb? ……g/dL	73
Final Dx available? 0 Yes 1 No	74
What was it? ……	

…… …… 0 | 7 | 14 1 | 8 | 15 2 | 9 | 16 3 | 10 | 17 4 | 11 | 18 5 | 12 | 19 6 | 13 | 20	1-6
Patient alive at discharge? 0 Yes 1 No	7
Comments: …… …… ……	
NHLS Laboratory Results:	
HIV Serology: 0 Positive 1 Negative 2 Indeterminate	8
Additional Testing: 0 Positive 1 Negative 2 Indeterminate	9
Comments: ……	

Appendix D – Draft letter of request to the CEO of the Port Elizabeth Hospital Complex

XX August 2012

Mr T Madonsela

Chief Executive Officer – Port Elizabeth Hospital Complex

Room B13

Walton Building

Connyngham Road

Port Elizabeth, 6057

Dear Mr Madonsela,

Request for permission to collect data at the Livingston Hospital for a Master's study titled: Transfusion Practices in the Eastern Cape Province of South Africa in the era of HIV and HAART.

As you are aware, I currently hold the position of Zone Medical Officer for the Eastern Cape for the South African National Blood Service. I am responsible for all clinical aspects relating to the collection, testing, processing and storage of blood and blood products as well as for Transfusion Medicine related issues and training in the province.

I am in the process of writing a thesis to obtain a Master's Degree in Medical Clinical Science (Transfusion) in the Faculty of Health Sciences at the University of the Free State (Student number: 1988511588). The title of my research is: *The HIV prevalence among and clinical speciality distribution of the recipients of blood and blood products in a referral hospital in the Eastern Cape Province of South Africa.*

My supervisor is:

Prof. V.J. Louw

Head: Division Clinical Haematology

Department of Internal Medicine

Faculty of Health Sciences

University of the Free State

Bloemfontein, South Africa

Co-supervisors:

Prof. E.L. Murphy

Professor, Department of Laboratory Medicine and Epidemiology/Biostatistics

University of California San Francisco

Senior Investigator, Blood Systems Research Institute

San Francisco, California, USA

Dr. L. Pretorius

Senior Lecturer

Department of Haematology and Cell Biology

Faculty of Health Sciences

University of the Free State

Bloemfontein, South Africa

The **purpose** of my research is to determine the overall HIV-prevalence among blood transfusion recipients as well as the transfusion practices in the hospitalised HIV-positive versus HIV-negative

population with a view to aiding blood collection services with procurement planning and health authorities with budget planning.

The **problem** that will be addressed through this research is the lack of knowledge regarding the overall blood requirements of the HIV-positive population, in particular what proportion of blood is being issued to HIV-positive patients and whether a doctor's transfusion practices are influenced by the patient's HIV status.

With this study we **aim** to determine the HIV prevalence among blood recipients as well as the transfusion practices in HIV-positive versus -negative patients. In addition we aim to establish the speciality distribution of the patients who receive blood and blood products.

The **objective** of this research is to study the prevalence of HIV amongst the patients receiving blood at a large public sector, referral hospital in Port Elizabeth and to review whether a patient's HIV status influences doctors' transfusion habits with a detailed analysis of the indication for transfusion as well as pre- and port transfusion haemoglobin levels.

As part of the process of developing and conducting the study we aim to cover the following objectives:

- Gain an understanding of the extent of the HIV pandemic and how it evolved in South Africa, in particular how it affected health resource utilisation such as bed occupancy and displacement of HIV-negative patients. This will be done through a literature review.

- Review and analyse the current overall blood utilisation in South Africa and how it has changed over time, specifically to assess whether changes in blood utilisation followed the trends of the HIV epidemic. This will be done through a literature review.

- Develop a deeper understanding of anaemia in HIV, in particular regarding the pathophysiology, causes, investigation and management. The aim being to understand whether there would be any reason for managing and transfusing HIV-positive patients differently to those who are HIV-negative. This will be done through a literature review

- Gather information on the transfusion habits of doctors in relation to both HIV-positive and –negative patients to evaluate the appropriateness of the care, with the aim of identifying areas of inappropriate care for which training and education can be developed.

Finally, all the information and data gathered will be collated and analysed to provide context to the prevalence of HIV/AIDS and how it influences prescriber habits, from which health authorities and blood bankers would be able to better plan health resource allocation.

Better understanding of current transfusion habits will inform future training and education requirements to ensure that doctors utilise this scarce resource in a rational and evidence based manner.

I am therefore requesting you to evaluate the attached protocol and to provide me with the necessary approval to collect the data required at the Livingstone Hospital during October to December 2012. You can contact me at the following numbers and address:

Telephone number: 041-391-8269

Cellular phone: 082 578 7045

Email address: karin.vandenberg@sanbs.org.za

Postal address: South African National Blood Services

Buckingham Road

Mount Croix

Port Elizabeth, 6001

South Africa

Please feel free to contact me should you have any queries on the protocol.

Yours respectfully,

Dr Karin van den Berg

South African National Blood Services

Port Elizabeth

(ECUFS No.: 194/2012)

Registered Project

Appendix E – Draft letter of request to the Medical Supervisor of the Livingstone Hospital

XX August 2012

Dr R May

Chief Medical Supervisor

Livingstone Hospital

Stanford Road

Korsten

Port Elizabeth, 6020

Dear Dr May,

Request for permission to collect data at the Livingston Hospital for a Master's study titled: Transfusion Practices in the Eastern Cape Province of South Africa in the era of HIV and HAART.

As you are aware, I currently hold the position of Zone Medical Officer for the Eastern Cape for the South African National Blood Service. I am responsible for all clinical aspects relating to the collection, testing, processing and storage of blood and blood products as well as for Transfusion Medicine related issues and training in the province.

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the recipients of blood and blood products in a referral hospital in the Eastern Cape Province of South Africa.

My supervisor is:

Prof. V.J. Louw

Head: Division Clinical Haematology

Department of Internal Medicine

Faculty of Health Sciences

University of the Free State

Bloemfontein, South Africa

Co-supervisors:

Prof. E.L. Murphy

Professor, Department of Laboratory Medicine and Epidemiology/Biostatistics

University of California San Francisco

Senior Investigator, Blood Systems Research Institute

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Dr. L. Pretorius

Senior Lecturer

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With this study we **aim** to determine the HIV prevalence among blood recipients as well as the transfusion practices in HIV-positive versus -negative patients. In addition we aim to establish the speciality distribution of the patients who receive blood and blood products.

The **objective** of this research is to study the prevalence of HIV amongst the patients receiving blood at a large public sector, referral hospital in Port Elizabeth and to review whether a patient's HIV status influences doctors' transfusion habits with a detailed analysis of the indication for transfusion as well as pre- and port transfusion haemoglobin levels.

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- Develop a deeper understanding of anaemia in HIV, in particular regarding the pathophysiology, causes, investigation and management. The aim being to understand whether there would be any reason for managing and transfusing HIV-positive patients differently to those who are HIV-negative. This will be done through a literature review

- Gather information on the transfusion habits of doctors in relation to both HIV-positive and –negative patients to evaluate the appropriateness of the care, with the aim of identifying areas of inappropriate care for which training and education can be developed.

Finally, all the information and data gathered will be collated and analysed to provide context to the prevalence of HIV/AIDS and how it influences prescriber habits, from which health authorities and blood bankers would be able to better plan health resource allocation.

Better understanding of current transfusion habits will inform future training and education requirements to ensure that doctors utilise this scarce resource in a rational and evidence based manner.

I am therefore requesting you to evaluate the attached protocol and to provide me with the necessary approval to collect the data required at the Livingstone Hospital during October to December 2012. You can contact me at the following numbers and address:

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Cellular phone: 082 578 7045

Email address: karin.vandenberg@sanbs.org.za

Postal address: South African National Blood Services

Buckingham Road

Mount Croix

Port Elizabeth, 6001

South Africa

Please feel free to contact me should you have any queries on the protocol.

Yours respectfully,

Dr Karin van den Berg

South African National Blood Services

Port Elizabeth

(ECUFS No.: 194/2012)

Registered Project

Appendix F – Draft letter of request to the Heads of Department at the Livingstone Hospital

XX August 2012

Dr T Ellis (Dr L van der Merwe; Dr S Pillay)

Head of Department

Department of Internal Medicine

Livingstone Hospital

Stanford Road

Korsten

Port Elizabeth, 6020

Dear Dr Ellis,

Request for permission to collect data at the Livingston Hospital for a Master's study titled: Transfusion Practices in the Eastern Cape Province of South Africa in the era of HIV and HAART.

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Faculty of Health Sciences

University of the Free State

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- Gather information on the transfusion habits of doctors in relation to both HIV-positive and –negative patients to evaluate the appropriateness of the care, with the aim of identifying areas of inappropriate care for which training and education can be developed.

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Yours respectfully,

Dr Karin van den Berg

South African National Blood Services

Port Elizabeth

(ECUFS No.: 194/2012)

Registered Project

Appendix G – Draft Letter of request to the Unit Managers at the Livingstone Hospital

XX August 2012

Sr XYZ

Unit Manager

Medical Ward

Livingstone Hospital

Stanford Road

Korsten

Port Elizabeth, 6020

Dear Sr XYZ,

Request for permission to collect data at the Livingston Hospital for a Master's study titled: Transfusion Practices in the Eastern Cape Province of South Africa in the era of HIV and HAART.

I currently hold the position of Zone Medical Officer for the Eastern Cape for the South African National Blood Service. I am responsible for all clinical aspects relating to the collection, testing, processing and storage of blood and blood products as well as for Transfusion Medicine related issues and training in the province.

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My supervisor is:

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Department of Internal Medicine

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Bloemfontein, South Africa

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Prof. E.L. Murphy

Professor, Department of Laboratory Medicine and Epidemiology/Biostatistics

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Senior Investigator, Blood Systems Research Institute

San Francisco, California, USA

Dr. L. Pretorius

Senior Lecturer

Department of Haematology and Cell Biology

Faculty of Health Sciences

University of the Free State

Bloemfontein, South Africa

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With this study we **aim** to determine the HIV prevalence among blood recipients as well as the transfusion practices in HIV-positive versus -negative patients. In addition we aim to establish the speciality distribution of the patients who receive blood and blood products.

The **objective** of this research is to study the prevalence of HIV amongst the patients receiving blood at a large public sector, referral hospital in Port Elizabeth and to review whether a patient's HIV status influences doctors' transfusion habits with a detailed analysis of the indication for transfusion as well as pre- and port transfusion haemoglobin levels.

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Yours respectfully,

Dr Karin van den Berg

South African National Blood Services

Port Elizabeth

(ECUFS No.: 194/2012)

Registered Project

Appendix H – Draft letter of request to the Medical Director and CEO of the South African National Blood Services

XX August 2012

Dr L Mpuntsha (Dr C Ingram)

Chief Executive Officer

South African National Blood Services

2 Constantia Boulevard

Constantia Kloof

Roodepoort, 1709

Dear Dr Mpuntsha,

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Senior Lecturer

Department of Haematology and Cell Biology

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Bloemfontein, South Africa

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Yours respectfully,

Dr Karin van den Berg

South African National Blood Services

Port Elizabeth

(ECUFS No.: 194/2012)

Registered Project

Appendix I – Draft letter of request to the Zone Technical Manager of the South African National Blood Services

XX August 2012

Mr C Scott

Zone Technical Manager

South African National Blood Services

Buckingham Road

Mount Croix

Port Elizabeth, 6001

Dear Mr Scott,

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University of the Free State

Bloemfontein, South Africa

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Professor, Department of Laboratory Medicine and Epidemiology/Biostatistics

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Senior Investigator, Blood Systems Research Institute

San Francisco, California, USA

Dr. L. Pretorius

Senior Lecturer

Department of Haematology and Cell Biology

Faculty of Health Sciences

University of the Free State

Bloemfontein, South Africa

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Yours respectfully,

Dr Karin van den Berg

South African National Blood Services

Port Elizabeth

(ECUFS No.: 194/2012)

Registered Project

Appendix J – Draft letter of request to the Blood Bank Supervisor of the Livingstone Blood Bank

XX August 2012

Mr O Orien

Blood Bank Supervisor

South African National Blood Services

Livingstone Hospital

Stanford Road

Korsten

Port Elizabeth, 6020

Dear Mr Orien,

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