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2021
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A STUDY OF HIV PRESENTATIONS TO AN ADULT EMERGENCY DEPARTMENT AND DEVELOPMENT AND VALIDATION OF AN OUTCOME PREDICTION MODEL

Abdullah Ebrahim Laher

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 2021

DECLARATION

I, **Abdullah Ebrahim Laher (student no. 9902884F)**, hereby declare that this thesis is my own work and has not been submitted or presented for any other degree or professional qualification at this or any other institute. This research was undertaken in the Division of Emergency Medicine, University of the Witwatersrand, Johannesburg, South Africa.

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DEDICATION

To Almighty Allah, my Creator, my Sustainer, the Mighty, the Kind, the Majestic, the Wise, the All-Knowing, ……. who has afforded me the opportunity and ability to serve others.

ACKNOWLEDGEMENTS

Firstly, all praises and thanks are due to Almighty ALLAH, the greatest teacher of all, for the countless blessings that He has undeservingly bestowed upon me.

I extend my utmost gratitude to *my parents, my wife Rookeya and my family* for their continual support, encouragement, motivation, unconditional support throughout, boundless sacrifices and immense patience over the years.

I express my extreme gratitude to my supervisors, *Professor GA Richards, Professor F Paruk and Professor WDF Venter* for their expertise, patience, motivation, guidance, insightful comments, immense experience, efficiency, proficiency, vast knowledge, and their confidence in me.

I am also enormously grateful to *Professor F Motara,* Head of the Division of Emergency Medicine, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital Emergency Department (CMJAH ED) and *Dr M Moolla,* specialist Emergency Physician at CMJAH ED, who are my seniors and have been my mentors over the years, for their kindness, unselfishness, continual support, guidance, invaluable advice, encouragement, leadership and motivation, especially at times when proceedings were at a halt and the going was tough.

I am also very grateful to *Dr OA Ayeni,* Faculty of Health Sciences, University of the Witwatersrand, for her expertise and assistance with statistical analysis and especially for her guidance and advice with regards to the development and validation of the outcome prediction model.

I express my thanks and am indebted to all the patients that volunteered and consented to study participation for their huge contribution to science and for being my teachers. I am also largely indebted to the doctors and nurses at CMJAH ED for their assistance with identifying potential

study participants. Finally, I am thankful to everybody that lent their weight and thereby contributed in any way to the completion and realization of this thesis.

JOURNAL PUBLICATIONS AND CONFERENCE PRESENTATIONS ARISING FROM THIS THESIS

Journal publications

1. Laher, A. E., Venter, W. D. F., Richards, G. A., & Paruk, F. (2021). Profile of presentation of HIV-positive patients to an emergency department in Johannesburg, South Africa. Southern African Journal of HIV Medicine, 22(1), 1177. https://doi.org/10.4102/sajhivmed.v22i1.1177
   Indexing: PubMed / Web of Science (Impact Factor 2.50) / Scopus (CiteScore 1.3)

2. Laher, A. E., Richards, G. A., Paruk, F., & Venter, W. D. F. (2021). Antiretroviral therapy non-adherence among HIV-positive patients presenting to an emergency department in Johannesburg, South Africa: Associations and reasons. South African Medical Journal, 111(8), 753-758. https://doi.org/10.7196/SAMJ.2021.v111i8.15604
   Indexing: PubMed / Web of Science (Impact Factor 1.31) / Scopus (CiteScore 1.8)

3. Laher, A. E., Paruk, F., Richards, G. A., & Venter, W. D. F. (2021). Predictors of prolonged hospital stay in HIV-positive patients presenting to the emergency department. PLOS ONE, 16(4), e0249706. https://doi.org/10.1371/journal.pone.0249706
   Indexing: PubMed / Web of Science (Impact Factor 2.74) / Scopus (CiteScore 5.2)

4. Laher, A., Paruk, F., Venter, W., Ayeni, O., & Richards, G. (2021). Predictors of in-hospital mortality among HIV-positive patients presenting with an acute illness to the emergency department. HIV Medicine, 22(7), 557-566. https://doi.org/10.1111/hiv.13097
   Indexing: PubMed / Web of Science (Impact Factor 3.55) / Scopus (CiteScore 5.8)

5. Laher, A. E., Paruk, F., Venter, W. D. F., Ayeni, O. A., Motara, F., Moolla, M., & Richards, G. A. (2021). Development and internal validation of the HIV In-hospital Mortality Prediction (HIV-IMP) risk score. HIV Medicine, 23(1), 80-89. https://doi.org/10.1111/hiv.13159
   Indexing: PubMed / Web of Science (Impact Factor 3.55) / Scopus (CiteScore 5.8)

Conference presentations

1. Laher, A. E., Venter, W. D. F., Richards, G. A., & Paruk, F. Profile of presentation of HIV-positive patients to an emergency department in Johannesburg, South Africa. University of the Witwatersrand School of Clinical Medicine (SOCM) research day, Johannesburg, South Africa. September 2021. (Poster presentation, P-15).

2. Laher, A. E., Richards, G. A., Paruk, F., & Venter, W. D. F. ART Non-adherence Among HIV-positive Patients Presenting to an Emergency Department in Johannesburg: Associations and Reasons. University of the Witwatersrand School of Clinical Medicine (SOCM) research day, Johannesburg, South Africa. September 2021. (Poster presentation P-16).

3. Laher, A. E., Paruk, F., Richards, G. A., & Venter, W. D. F. Predictors of prolonged hospital stay in HIV-positive patients presenting to the Emergency Department. University of the Witwatersrand School of Clinical Medicine (SOCM) research day, Johannesburg, South Africa. September 2021. (Poster presentation P-14).

4. Laher, A. E., Paruk, F., Venter, W. D. F., Ayeni, O. A., & Richards, G. A. Predictors of in-hospital mortality among HIV-positive patients presenting with an acute illness to the ED. University of the Witwatersrand School of Clinical Medicine (SOCM) research day, Johannesburg, South Africa. September 2021. (Oral presentation SOCM7B- 01).

5. Laher, A. E., Paruk, F., Venter, W. D. F., Ayeni, O. A., Motara, F., Moolla, M., & Richards, G. A. (2021). Development and internal validation of the HIV In-hospital Mortality Prediction (HIV-IMP) risk score. University of the Witwatersrand School of

Clinical Medicine (SOCM) research day, Johannesburg, South Africa. September 2021. (Poster presentation P-17).

6. Laher, A. E., Paruk, F., Venter, W. D. F., Ayeni, O. A., Motara, F., Moolla, M., & Richards, G. A. (2021). Development and internal validation of the HIV In-hospital Mortality Prediction (HIV-IMP) risk score. 40th International Symposium on Intensive Care & Emergency Medicine (ISICEM), Brussels, Belgium. September 2021. (Poster presentation P-202).

SUBMISSION FORMAT OF THIS RESEARCH REPORT

The style guide for theses, dissertations and research reports of the Faculty of Health Sciences, University of the Witwatersrand describes several formats that are acceptable for submission of a PhD thesis (https://www.wits.ac.za/media/wits-university/faculties-and-schools/health-sciences/research-entities/documents/FACULTY%20OF%20HEALTH%20SCIENCES%20STYLE%20GUIDE%20FOR%20THESES-DISSERTATIONS-AND-RESEARCH%20REPORTS-Updated%20Marh%202016.pdf).

This PhD thesis is being submitted in the 'integrated' format and is comprised of eight chapters. Chapters one and two comprises the literature review and the study aims and objectives respectively. Chapters three to seven comprises each of the five articles that emanated from this research project, all of which have been published in accredited peer-reviewed journals that are indexed in major databases that include PubMed, Web of Science and Scopus. The concluding chapter (chapter 8) comprises the integrated discussion, study limitations and study conclusions.

Since the study methodology has been individually described in each of the five articles, hence, to limit unnecessary repetition and redundancy, an integrated 'methods' chapter was not included. References have been presented in the Harvard style of referencing and appear at the end of each of the relevant chapters in this thesis. For the sake of uniformity, the referencing style in each of the published articles were converted from the respective journal referencing style to the Harvard style of referencing. Additionally, grammar and language throughout the entire thesis was formatted to the "English (South Africa)" style. Furthermore, subheadings, tables, and figures in each of the published articles were renumbered to maintain continuous numbering throughout the document, as reflected in the table of contents, list of tables and list of figures sections. Besides these modifications, each of the published articles have been presented in word format in the version that was accepted by the respective journals.

ABSTRACT

Background: Human immunodeficiency virus (HIV) infection is a global epidemic that has affected approximately 38 million people worldwide. In 2019, HIV ranked as the 3rd highest cause of global mortality. In 2019, there were approximately 1.7 million new cases of HIV with 690 000 HIV related deaths. Sub-Saharan Africa is home to approximately two-thirds of people living with HIV (PLWH). South Africa has an estimated 7.5 million PLWH, which is more than twice that of any other country in the world and equates to approximately one-fifth of the global burden of the disease. It is estimated that 92% of PLWH in South Africa are aware of their status, 70% are on anti-retroviral therapy (ART) and 64% are virally suppressed.

Objectives: This study aimed to 1) describe the patterns of presentation of HIV-positive patients presenting to an emergency department (ED), 2) determine the rates of ART non-adherence and its associations and the reasons for ART non-adherence in these patients, 3) determine the predictors of prolonged hospital length of stay (LOS) in these patients , 4) determine the predictors of in-hospital mortality in these patients, and 5) develop and internally validate a predictive model that will be capable of reasonably predicting in-hospital mortality in HIV-positive patients presenting with an acute illness.

Methods: This was a prospective study that enrolled consecutive HIV-positive patients that presented to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) adult ED between 07 July 2017 and 18 October 2018. Self-reported adherence was assessed using the AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ). Data was also subjected to univariate and multivariate logistic regression to determine parameters associated with a higher likelihood of hospital LOS ≥7 days and a higher likelihood of in-hospital mortality. For the development of the HIV in-hospital mortality prediction (HIV-IMP) model, multivariate logistic regression was used to determine parameters for inclusion while model discrimination and calibration were assessed by means of the area under the receiver operating curve (AUROC) and the Hosmer–Lemeshow goodness-of-fit test, respectively. Internal validation was conducted using the regular bootstrap technique.

Results: A total of 1224 participants were enrolled in the study. HIV was newly diagnosed in 212 (17.3%), 276 (22.5%) had bacterial pneumonia, 244 (19.9%) had tuberculosis (TB), 86 (7.0%) had gastroenteritis, 205 (16.7%) required intensive care unit admission, CD4 cell count

was < 100 cell/mm^3 in 527 (47.6%), HIV viral load (VL) was > 1000 copies/mL in 619 (59.0%), haemoglobin was < 11 g/dL in 636 (56.3%), creatinine was > 120 μmol/L in 294 (29.3%), lactate was > 2 mmol/L in 470 (42.0%) and albumin was < 35 g/L in 633 (60.8%). Of the 761 (75.2%) study participants that were on ART at the time of ED presentation, 245 (32.2%) were non-adherent as per the ACTG-AQ. Participants not yet on ART prior to ED presentation demonstrated a significantly higher in-hospital mortality than participants on ART (OR 1.69, p =0.002). Younger age, male sex, CD4 <100 cell/mm^3, lack of viral suppression, a high NEWS-2 score (≥7 points), and length of hospital stay ≥7 days were significantly associated with ART non-adherence (p <0.05). Forgetfulness (13.9%), lack of social support, depression/ stress/ mental illness, and lack of transport money to collect medications (9.9% each) were the commonest reasons for ART non-adherence. The median (IQR) hospital LOS was 4.9 (3.5-8.0) days, while the mean (SD) LOS was 6.6 (8.3) days. A total of 381 (31.1%) participants were admitted for ≥7 days. On multivariate analysis of the data, haemoglobin <11 g/dL (OR 1.37, p =0.032), Glasgow coma scale (GCS) <15 (OR 1.80, p =0.001), creatinine >120 μmol/L (OR 1.85, p =0.000), cryptococcal meningitis (OR 2.45, p =0.015) and bacterial meningitis (OR 4.83, p =0.002) were significantly associated with a higher likelihood of hospital LOS ≥7 days, while bacterial pneumonia (OR 0.35, p =0.000) and acute gastroenteritis (OR 0.40, p =0.025) were significantly associated with a lower likelihood of hospital LOS ≥7 days. A total of 166 (13.6%) participants died. On further multivariate analysis of the data, respiratory rate >20 breaths/min (OR 1.90, p =0.012], creatinine >120 mmol/L (OR 1.97, p =0.006), oxygen saturation <90% (OR 2.09, p =0.011), white cell count <4.0 9 10^9/L (OR 2.09, p =0.008), ART non-adherence or not yet on ART (OR 2.39, p =0.012), Glasgow Coma Scale <15 (OR 2.53, p =0.000), albumin <35 g/L (OR 2.61, p =0.002), lactate >2 mmol/L (OR 4.83, p =0.000) and cryptococcal meningitis (OR 6.78, p =0.000) were significantly associated with in-hospital mortality. Apart from cryptococcal meningitis, the remaining eight of these predictors of in-hospital mortality were included in the final HIV-IMP risk score. After internal validation, the model maintained good discrimination (AUROC 0.83, 95% confidence interval (CI) 0.78 – 0.88) and calibration (Hosmer-Lemeshow $\chi 2$ 2.26, p = 0.895).

Conclusions: Among HIV-positive patients presenting to the CMJAH ED, there was a high prevalence of opportunistic infections, a high prevalence of patients who were either not yet initiated on ART or were ART non-adherent, a high proportion of patients that required

prolonged hospital LOS and a relatively high proportion of patients that demised during the course of hospital admission. Various clinical and laboratory parameters were found to be useful in predicting prolonged hospital LOS and in-hospital mortality. These parameters may be of value in guiding clinical decision-making, directing the appropriate allocation of resources, and influencing patient disposition. The HIV-IMP risk score that was developed demonstrated overall good discrimination and calibration and is relatively easy to use.

Keywords

Human immunodeficiency virus; HIV; emergency department; ED; antiretroviral therapy; ART; adherence; non-adherence; CD4 cell count; HIV viral load; opportunistic infection; hospital admission; prolonged hospitalization, hospital length of stay; LOS; acute illness; in-hospital mortality; outcome prediction model; risk score; AUROC; calibration; discrimination

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LIST OF ABBREVIATIONS

AIDS – acquired immune deficiency syndrome
aHR – adjusted hazard ratio
aRR – adjusted relative risk
ART – antiretroviral therapy
CD4 – cluster of differentiation 4
CDC – Centers for Disease Control and Prevention
CI – confidence interval
DNA – deoxyribonucleic acid
HIV – human immunodeficiency virus
HR – hazard ratio
HTLV – human T-cell lymphotropic virus
ICU – intensive care unit
LOS – length of stay
MDR – multidrug resistant
mRNA – messenger ribonucleic acid
OR – odds ratio
PEP – post exposure prophylaxis
PLWH – people living with human immunodeficiency virus
PJP – pneumocystis jirovecii pneumonia
RNA – ribonucleic acid
TB – tuberculosis
UNAIDS – joint United Nations program on acquired immune deficiency syndrome
USA – United States of America
VL – viral load
XDR – extensively drug resistant
WHO – World Health Organization

CHAPTER 1: LITERATURE REVIEW

1.1 Introduction

Sub-Saharan Africa has the highest prevalence of HIV in the world, housing more than two-thirds of the 38 million cases globally. South Africa has an estimated 7.5 million people living with HIV (PLWH), i.e., more than any other country in the world. In 2019, it was estimated that approximately 19% of South Africans over the age of 15 years were HIV-positive while approximately 690 000 people died from HIV related illnesses in the same year ("List of countries by HIV/AIDS adult prevalence rate," 2020, "UNAIDS Data 2020," 2020). HIV currently ranks as the 3rd highest cause of global mortality, after cardiovascular disease and cancer ("Top 10 leading causes of death in the world from 1990-2019 complete ranking," 2019).

The widespread availability of safer antiretroviral therapy (ART) regimens over recent years has resulted in a substantial reduction in the overall HIV related morbidity and mortality (Trickey et al., 2017), with there being a 47% reduction in new HIV infections and a 40% reduction in HIV-related deaths in South Africa from the 2010 to 2019. However, with approximately 200 000 new HIV infections and 72 000 HIV-related deaths in 2019, the burden of the ongoing HIV epidemic in South Africa remains high ("UNAIDS Data 2020," 2020). Of further concern is that despite ART being made freely available to all South Africans with HIV as of September 2016 and irrespective of their CD4 cell count (Cullinan, 2016), approximately 30% of HIV-positive citizens are not yet on ART, while 36% of those on ART are not virally suppressed ("UNAIDS Data 2020," 2020).

Although the life expectancy of South Africans on ART has reportedly increased to approximately 80% of normal life expectancy (Johnson et al., 2013), our emergency departments (ED) and hospitals continue to encounter a high burden of HIV-related admissions (Meintjes et al., 2015). Compared to HIV-negative patients, those with HIV place a significant strain on healthcare resources as they have higher rates of hospitalisation, require longer length of hospital stay and have poorer clinical outcomes (Krentz et al., 2006). In fact, a large proportion of the

overall financial burden related to HIV has been attributed to the cost of in-hospital care and treatment of acutely ill HIV-positive patients (Barbour et al., 2009; Jones et al., 2019).

Among individuals on ART, ART non-adherence with subsequent virological and immunological failure is by far the commonest reason for clinical progression of disease and eventual requirement for hospitalization (Simoni et al., 2003). Commonly reported reasons for ART non-adherence among PLWH include poor insight relating to HIV and its treatment, forgetfulness, intolerable side effects, "stock-out" at facilities dispensing ART, high pill burden, no transport money to collect their medication, depression and poor social support (Essomba et al., 2015; Oku et al., 2013). Since most studies relating to ART non-adherence were predominantly conducted in out-patient clinic settings, obtaining similar data from patients presenting to the emergency department (ED) may be of value in developing additional strategies to improve ART uptake and adherence at various levels.

Furthermore, previous studies have demonstrated that various clinical and laboratory parameters such as the presenting diagnosis, requiring admission to the intensive care unit (ICU), low CD4 cell count, elevated HIV viral load (VL), anaemia, renal dysfunction, albuminemia, hyperlactatemia etc. have been associated with poorer outcomes in HIV-positive patients (Franceschini et al., 2005; Kerkhoff et al., 2015; Maphula et al., 2020; Siedner et al., 2014; Sudfeld et al., 2013; Tantisiriwat et al., 2001). However, none of these studies were exclusively conducted in the ED setting. In addition to guiding timely management that may include the early initiation of empiric antimicrobial therapy, judicious haemodynamic resuscitation, fast-tracking of special investigations and early ICU admission, the prompt identification of factors associated with poor outcomes at ED presentation may also assist clinicians with the appropriate channelling of resources and particularly in environments where these are limited.

Predicting outcomes in medical patients is not an easy task. Outcome prediction in medicine may be either subjective or objective. Although subjective ('gut feel") outcome prediction is widely used in daily practice, it is prone to human error (Kassirer and Gorry, 1978). Objective outcome prediction models may provide clinicians with significant adjunctive information. Validated outcome prediction scoring tools provide clinicians with additional information that

may be useful when counselling patients and their families and thereby enhancing patient/ family satisfaction and reducing the risk of litigation. Other advantages may include the selection of appropriate therapeutic strategies, better allocation of resources, timely initiation of palliative care, appropriate patient recruitment in research trials and a means of measuring and comparing unit performance (Paruk, 2007). Various outcome prediction models have been developed in select population groups that are in common use (Knaus et al., 1985; Seymour et al., 2016; Vincent et al., 1996), however, thus far there are no mortality prediction models for use in HIV-positive patients requiring acute hospital admission.

Hence, the purpose of this research project was to study the presentation of HIV-positive patients to the ED, with a particular focus on ART non-adherence, factors influencing hospital length of stay (LOS), factors influencing in-hospital mortality and finally the development and validation of a mortality prediction model for use in HIV-positive patients requiring hospital admission.

1.2 Origin, basic microbiology, and transmission of HIV

Human retroviruses are a family of enveloped viruses that contain an RNA (ribonucleic acid) genome together with the enzyme reverse transcriptase (RNA dependant DNA [deoxyribonucleic acid] polymerase) which is responsible for converting RNA into DNA to allow it to integrate into the host DNA (Smith and Daniel, 2006). Currently, there are only 6 retroviruses that are known to infect humans. These are human immunodeficiency virus type 1 (HIV-1), HIV-2, human T-cell lymphotropic virus type 1 (HTLV-1), HTLV-2, HTLV-3, and HTLV-4. HIV-1 and HIV-2 are two types of HIV that belong to the genus Lentivirus and are distinct from each other. HIV-1 is by far the most common of the two types and is also more virulent, more infectious and has a higher prevalence compared to HIV-2 which is predominantly concentrated in West Africa (Gilbert et al., 2003).

HIV-1 and HIV-2 are thought to have crossed over from chimpanzees and sooty mangabeys, respectively to humans in the 1920's (Sharp and Hahn, 2011). It was first clinically recognised in clusters of gay men and injection drug users in the United States of America (USA), who presented with features of Pneumocystis jirovecii pneumonia (PJP) (Gottlieb, 2006). Following several names changes, in 1986 the virus was finally named HIV (Basavapathruni and Anderson,

2007). Since HIV-1 is by far the more prevalent of the two types, the term HIV generally refers to HIV-1, which is responsible for the global HIV epidemic. HIV-1 has been divided into a major group (Group M) and three minor groups (Group N, O and P). The minor groups are predominantly confined to West and Central Africa. Group M is the most common group responsible for approximately 90% of HIV infections and is further subdivided into subtypes (A-L), some of which are even further subdivided into sub-subtypes. Subtype C is the most prevalent form in Southern Africa, Eastern Africa, India, Nepal, and parts of China ("HIV strains and types," 2019, "Subtypes of HIV," 2021).

The diameter of the HIV virion is approximately 60 times smaller in size than a red blood cell. The virion has two copies of single-stranded RNA that is enclosed by the capsid that comprises approximately 2000 copies of the p24 viral protein. RNA is tightly bound to p7 (nucleocapsid proteins) and is surrounded by several enzymes that include reverse transcriptase, integrase, ribonuclease, and proteases that are necessary for the replication and function of the virus. The capsid is encompassed by a protein matrix (p17) and a lipid membrane that is derived from the human host cell when the virus particle buds from the cell. The lipid membrane also contains several envelope glycoprotein complexes, each of which is made up of a cap (gp120) and a stem comprising of three gp41 molecules that fixes the complex into the viral envelope ("HIV Sequence Compendium 2008," 2008; Pancera et al., 2010). The envelope glycoprotein complex allows for the attachment and fusion of the viral envelope to the target cell membrane, thereby facilitating the release of viral contents into the host cell and initiation of the infectious cycle (Chan et al., 1997; Klein and Bjorkman, 2010). The structure of the HIV virion is depicted in figure 1 below.

Sexual intercourse is the most common mode of transmission of HIV from person to person through contact with blood, pre-ejaculate fluid, semen, and vaginal fluid. The presence of sexually transmitted genital ulcers substantially increases the risk of HIV transmission. Vertical transmission of HIV, also known as mother-to-child-transmission (MTCT) can occur from an infected mother to her baby during the course of pregnancy, during delivery or through breast milk and is responsible for the majority of infections in children. Rarer modes of transmission

include blood transfusion, organ donation and needlestick injuries (Aigbodion et al., 2019; Cohn and Clark, 2003; McDowall and Laher, 2019).

HIV can infect a number of immune cells including CD4 T cells, macrophages, microglial cells and dendritic cells (Clapham and McKnight, 2001). Macrophage-tropic (M-tropic) strains, the most common type, enters into cells through the CCR5 chemokine receptor that is predominantly expressed on memory T-cells, macrophages, and immature dendritic cells while T-cell tropic (T-tropic) strains enters into cells through the CXCR4 chemokine receptor which is primarily expressed on T-cell lines, whereas dual-tropic strains are able to use both CCR5 and CXCR4 as co-receptors for viral entry. Hence individuals harbouring the CCR5 delta 32 mutation, which is most commonly found among people of Northern European descent, are resistant to HIV infection by the M-tropic strain (Coakley et al., 2005; Deng et al., 1996).

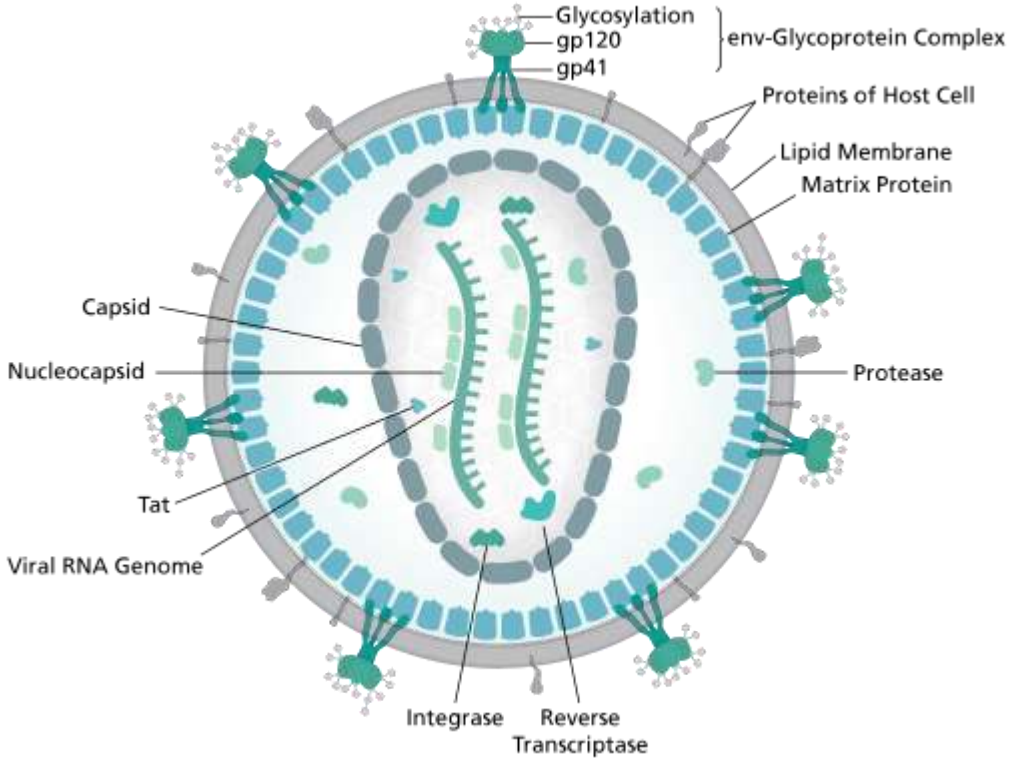


Figure 1: Structure of the HIV virion
Image obtained from Splettstoesser T. HI-virion-structure en.svg. 2014. https://en.wikipedia.org/wiki/File:HI-virion-structure_en.svg. Distributed under the terms of the Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by-sa/4.0/deed.en). No changes have been made to the image.

1.3 Replication cycle of the HIV virion

Figure 2 describes the basics of the HIV virions replication cycle. The HIV virion enters CD4 T cells and macrophages by the initial interaction of gp120 with the target cell chemokine co-receptor (either CCR5 or CXCR4). This leads to fusion of the viral membrane with the target cell membrane and subsequent entry of the viral capsid along with its contents that include the single-stranded HIV RNA genome as well as several enzymes such as reverse transcriptase, ribonuclease, integrase, and protease. Thereafter, through the process of reverse transcription, which is orchestrated by the enzyme reverse transcriptase, the RNA genome is transcribed into double-strand DNA (Chan and Kim, 1998). This process is extremely error-prone and frequently results in mutations that are responsible for the development of drug resistance (Berkhout, 2001).

With the aid of the enzyme integrase, the viral DNA is thereafter integrated into the host genome where it enters the latent phase and may lie dormant for a period of time (Zheng et al., 2005). Upregulation of nuclear factor kappa B (NF-κB) and other transcription factors that coincides with T-cell activation during intercurrent infection serves to reactivate viral replication. Hence, T-cells that are actively fighting infection are more likely to be targeted and destroyed by the HIV virus (Hiscott et al., 2001).

During viral replication, viral DNA is transcribed into RNA. Some of the newly replicated RNA is then spliced to produce copies of messenger RNA (mRNA), which are exported into the cytoplasm and translated to produce the regulatory proteins Tat and Rev. Tat functions to encourage the production of new virus while Rev travels back into the nucleus, where it facilitates unspliced copies of viral RNA to leave the nucleus (Charnay et al., 2009; Pollard and Malim, 1998). Some of these unspliced RNA serve as viral copies, while others serve as mRNA that are translated into Gag and Env, both of which are structural proteins for the newly formed virus (Butsch and Boris-Lawrie, 2002).

Assembly and release of the newly formed HIV-1 virion takes place at the host cell membrane and concludes the steps of the viral cycle. The Env polyprotein (gp160) is cleaved to form gp41 and gp120, the envelope glycoproteins (Hallenberger et al., 1992) which are then transported to and anchored on the host plasma membrane. The HIV RNA along with the packaged viral

proteases and components of the host cell membrane begins to bud from the host cell as the forming virion which is immature at this stage. The various structural components thereafter assemble to produce mature virions outside the host cell (Ivanchenko et al., 2009).

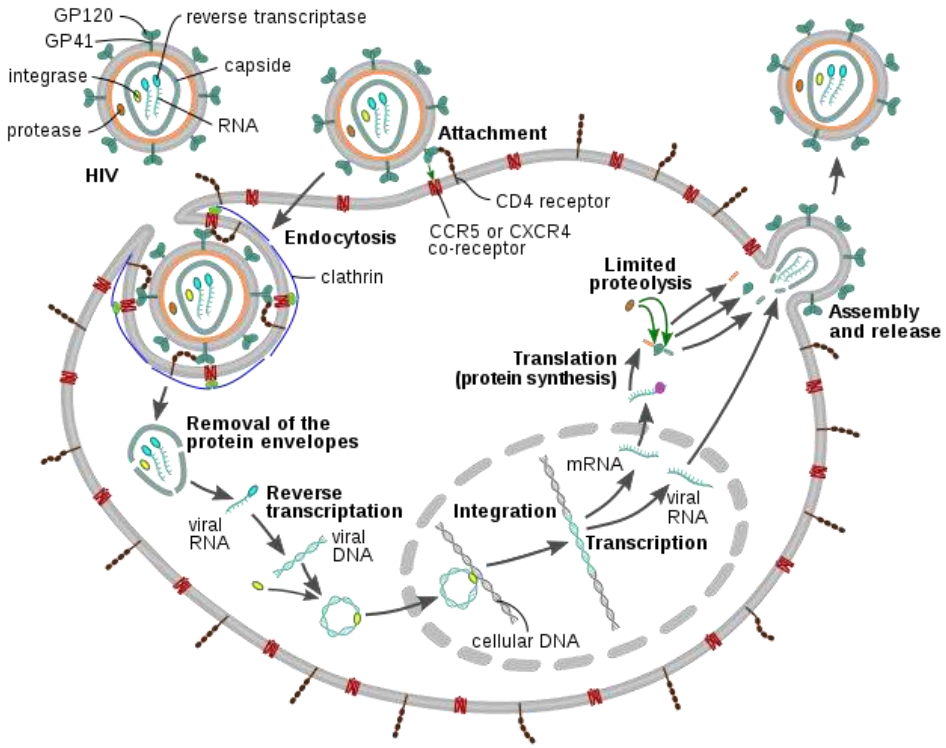


Figure 2: Simplified diagram describing the replication cycle of the HIV virion
Image obtained from Splettstoesser T. HIV-replication-cycle-en.svg. 2017. https://en.wikipedia.org/wiki/File:HIV-replication-cycle-en.svg. Distributed under the terms of the Creative Commons Attribution-Share Alike 3.0 Unported (https://creativecommons.org/licenses/by-sa/3.0/deed.en). No changes have been made to the image.

There are two mechanisms that the HIV virus may use to spread within the human body. The first being cell-free spread, where free virions enter and infect other T cells after having undergone viral replication and being released from infected CD4 cells (Zhang et al., 2015). The second mechanism of spread is described as cell-to-cell spread, which entails direct transmission of virions from one cell to another either by means of virological synapses between CD4 cells or presentation to CD4 cells by antigen-presenting cells such as macrophages or dendritic cells (Sattentau, 2008). The rapid rate of replication of the HIV virus (approximately 10^{10} virions

daily) together with a high rate of viral mutation translates to the presence of multiple variants of the virus in a single host (Rambaut et al., 2004).

There are several mechanisms through which HIV causes a reduction in the CD4 cell count. These include apoptosis (programmed cell death) of uninfected cells, pyroptosis (inflammatory form of programmed cell death) of infected cells, direct killing of infected cells by the virus and killing of infected cells by CD_8 cells. Untreated, the HIV virus will continue to multiply (increasing HIV VL) with a resultant decrease in the CD4 cell count, thereby promoting the onset of AIDS and increasing the host susceptibility to opportunistic infections (Doitsh et al., 2014; Garg et al., 2012; Young et al., 2008). Survival without ART is largely dependent on the HIV subtype, however, most individuals die within approximately 10 years of acquiring the infection ("AIDS epidemic update," 2007). The relationship between the HIV VL and CD4 cell count over the course of untreated HIV is described in figure 3.

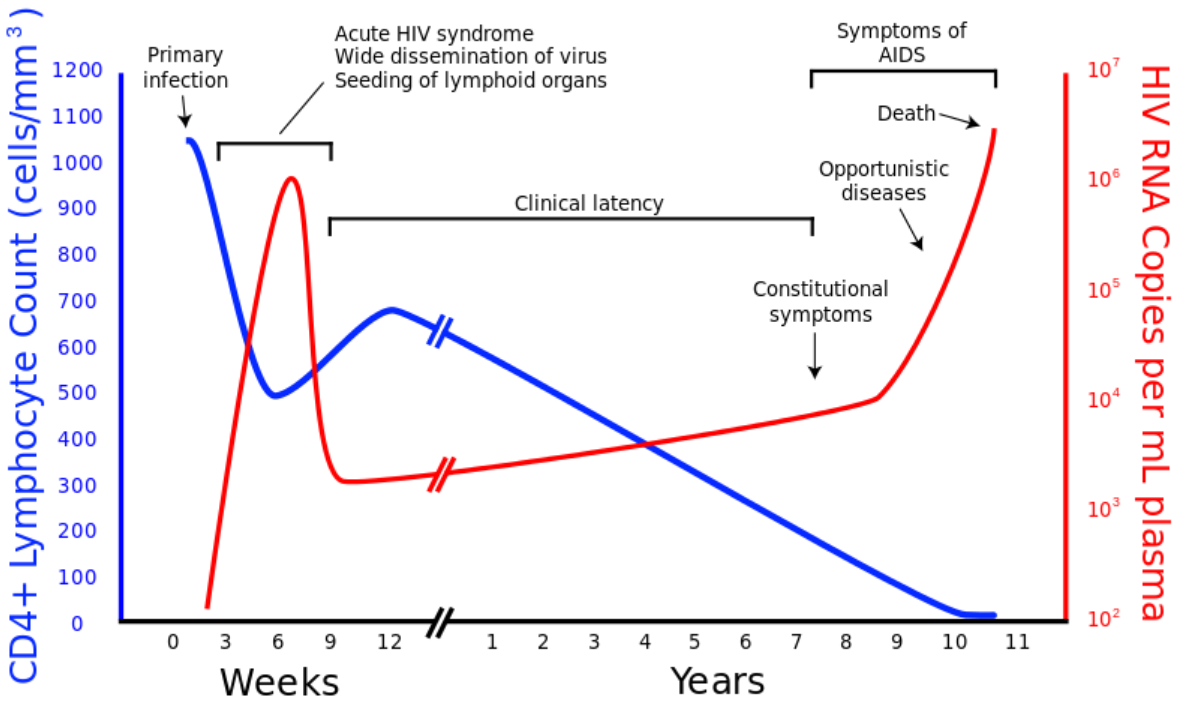


Figure 3: The average relationship between the HIV VL and CD4 cell count over the course of untreated HIV. This may vary from patient to patient
Image obtained from Hiv-timecourse copy.svg. 2011. https://en.wikipedia.org/wiki/File:Hiv-timecourse_copy.svg. Distributed under the terms of the Creative Commons CC0 1.0 Universal Public Domain Dedication (https://creativecommons.org/publicdomain/zero/1.0/deed.en). No changes have been made to the image.

1.4 Diagnosis

HIV tests are capable of detecting the presence of HIV antibodies, antigens, or RNA (also known as nucleic acid testing (NAT)) in serum, saliva, or urine. The window period (duration from onset to when the test is capable of diagnosing the infection) is approximately three to six weeks for antibody testing, 16 days for antigen-based tests and 12 days for NAT (Hurt et al., 2017). According to the Joint United Nations Program on AIDS (UNAIDS) and World Health Organization (WHO) policy statement on HIV Testing, HIV testing must be confidential, conducted with informed consent and must include counselling for those testing positive ("UNAIDS/WHO policy staement on HIV testing," 2004). The sequence of appearance of various laboratory markers for HIV-1 infection is described in figure 4.

1.4.1 Antibody tests

HIV antibody tests are generally cheap, accurate and are routinely used as first line tests for the diagnosis of HIV in adults. The window period of HIV, which is defined as the interval from the onset of infection to the production of measurable antibodies (seroconversion), may range between three weeks and six months. Most individuals develop measurable antibodies within one month of infection, with 97% developing detectable antibody levels within three months of being infected. Although HIV testing conducted during the window period may produce a false negative result, infected persons can transmit the virus to others during the window period ("HIV Testing Basics for Consumers," 2010).

Enzyme-linked immunosorbent assay

The enzyme-linked immunosorbent assay (ELISA), or enzyme immunoassay (EIA), is highly sensitive, relatively cheap and was the original diagnostic tool employed for the diagnosis of HIV. Serum samples are subjected to a 400-fold dilution and then applied to a plate containing HIV antigens. A secondary antibody that is linked to an enzyme is thereafter added. These antibodies then bind to serum HIV antibodies (if present) that are bound to the plated HIV antigens. After undergoing washing, a substrate for the enzyme is applied, the catalysis of which leads to a change in colour which signifies the presence of secondary antibody binding to serum HIV antibodies, thereby confirming the diagnosis of HIV infection (Smith et al., 1991).

Western Blot

Similar to the ELISA test, the Western blot also detects the presence of viral antibodies. Viral proteins (gag, pol and env) produced by means of the recombinant immunoblot assay technique are first placed onto a gel medium and separated by application of an electric current. The proteins are then transferred to a membrane prior to application of diluted patient serum and thereafter allowing for patient antibodies (if present) to bind to the HIV protein (Healey et al., 1992).

HIV rapid/ point of care testing

These are qualitative immunoassays that are usually used as a part of multi-test algorithms for the diagnosis of HIV. With rapid bedside antibody methods (lateral flow chromatography assay) results are generally available within 15 – 30 minutes of testing. Tests used for the diagnosis of HIV must have both a high sensitivity and specificity. Hence, in general, most testing algorithms recommend that a positive test be confirmed with a second test from a different manufacturer. In cases where the initial rapid test is positive, but the confirmatory test negative, a blood sample should be sent to the laboratory for HIV ELISA testing, Western blot testing or other methods of testing. Similar to the ELISA test, HIV antibodies must reach detectable levels for a positive test (Greenwald et al., 2006).

1.4.2 Antigen tests

Antigen tests detect the presence of the HIV p24 capsid protein in the blood specimen. Since the p24 antigen is generally detectable before HIV antibodies, 4th generation assays frequently combine detection of p24 antigen and HIV antibodies in a single test and thereby allow for shortening of the window period to two to six weeks. Monoclonal antibodies targeted at the HIV p24 capsid protein are added to blood drawn from the patient. Similar to the ELISA test, another enzyme-linked antibody is thereafter added and binds to the monoclonal antibody – p24 protein complex (when present) thereby causing a colour change. It is not recommended that the p24 antigen test be used in isolation as antigen levels decrease with production of host antibodies, thereby reducing the sensitivity of the test beyond the early period of infection (Faraoni et al., 2013).

1.4.3 Nucleic acid testing

Nucleic acid tests detect sequences of gag, env and pol genes of the HIV virus. Although the window period for the diagnosis of HIV is significantly shortened with nucleic acid testing, the test is relatively expensive. Hence, in practice the nucleic acid test is predominantly used for testing of donor blood (Defoort et al., 2000; Fiebig et al., 2003).

1.4.4 HIV viral load

The HIV viral load test detects HIV RNA and is predominantly used to monitor a patient's response to ART. However, the test may also be used to diagnose HIV, to confirm the diagnosis of HIV following a reactive ELISA test and to resolve findings of indeterminate HIV tests (Kaplan, 2019).

1.4.5 HIV testing algorithm in South Africa

Based on the population prevalence of HIV, various testing algorithms are in use internationally. The South Africa National Department of Health (DoH) HIV testing algorithm recommends the use of approved HIV rapid tests as the basis for diagnosing HIV in adults and children ≥18 months. As per the algorithm, if the screening test is non-reactive, the result is reported as HIV negative with no need to perform a second confirmatory test, however, the possibility of a false negative test due to the window period must be considered. If the screening rapid test is reactive, a second confirmatory rapid test from a different manufacturer is then performed and if also reactive, the result is reported as HIV positive. In the event of discordant results where the screening test is reactive and confirmatory test non-reactive, the algorithm is immediately repeated. If both repeat tests are reactive, the HIV result is reported as positive and if both tests are negative, the HIV result is reported as negative. However, if both tests are still discordant, whole blood must be collected and sent to the laboratory for serial fourth generation ELISA testing. If both ELISA result are non-reactive, the HIV result is reported as negative and if both are reactive, the HIV result is reported as positive. However, if both ELISA tests are discordant, the result is reported as HIV inconclusive and the patient must be asked to return in six weeks for a repeat test ("National consolidated guidelines for the prevention of mother-to-child

transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults," 2015).

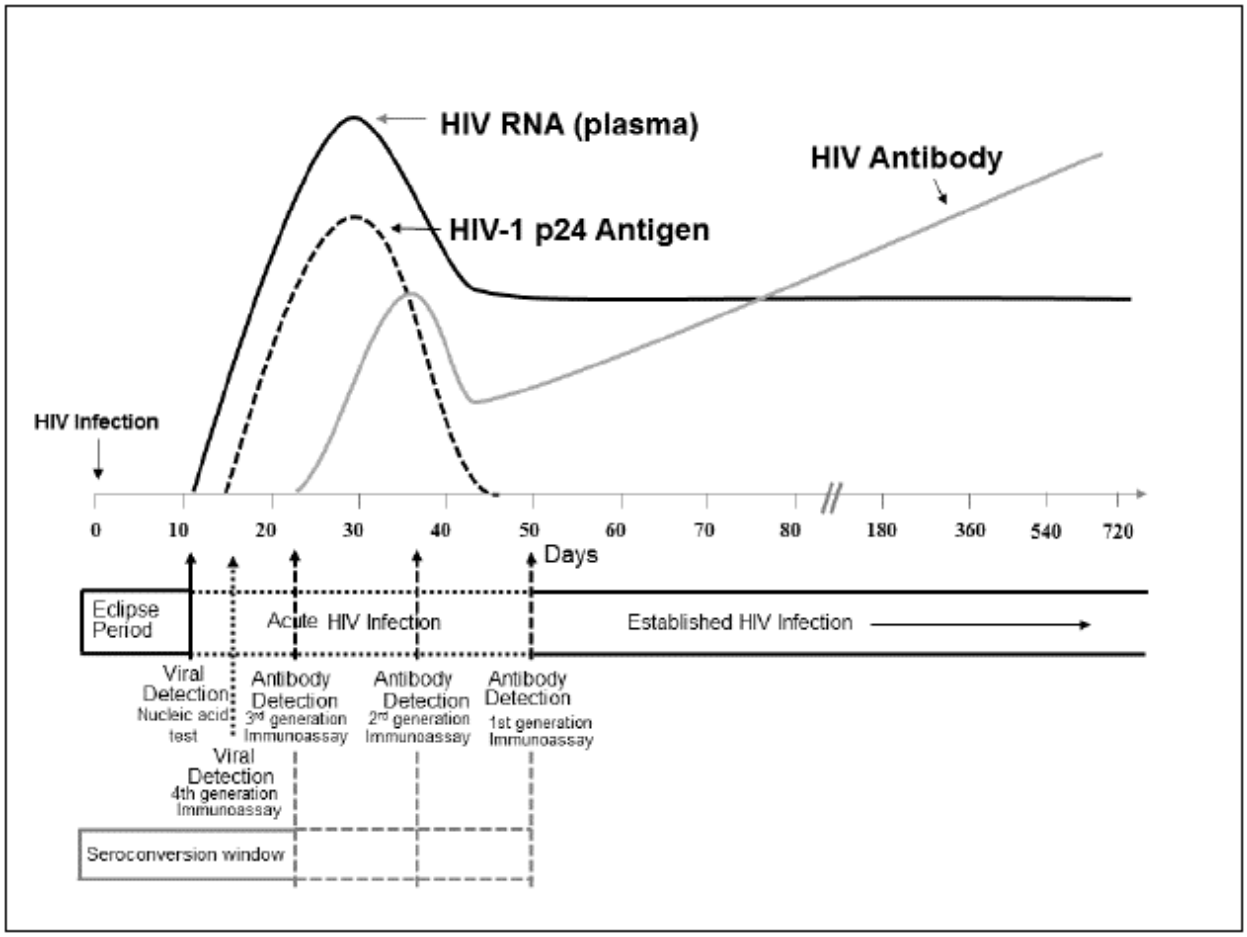


Figure 4: Sequence of appearance of laboratory markers for HIV-1 infection.
Note that units for vertical axis are not noted because their magnitude differs for RNA, p24 antigen, and antibody.
Image reproduced from Laboratory Testing for the Diagnosis of HIV Infection: Updated Recommendations – Centers for Disease Control and Prevention and Association of Public Health Laboratories. 2014. http://stacks.cdc.gov/view/cdc/23447. PHIL Image Reuse Terms and Conditions (https://www.cdc.gov/other/imagereuse.html). No changes have been made to the image.

1.5 Treatment of HIV

ART was first introduced in 1987 at a cost of over $10 000 per annum (Sonenklar, 2011).

Several studies such as NA-ACCORD, START and TEMPERANO showed that patients starting ART at an earlier stage and while the CD4 cell counts was higher, had better overall outcomes

and survival (Danel et al., 2015; Kitahata et al., 2009; Lundgren et al., 2015). People initiating ART late, when the CD4 cell count was lower, had less recovery of the immune system (Kelley et al., 2009).

Since ART reduces the HIV VL in blood as well as in genital secretions, the early initiation of ART has been shown to reduce the transmission of HIV between partners. A study reported a 96% reduction in the transmission of HIV in patients that were on ART (Cohen et al., 2016). In July 2016, the Prevention Access Campaign produced a consensus document that was endorsed by 400 organisations across 58 countries. The document stated that persons with an undetectable VL for greater than six months are at negligible risk of transmitting the virus to their sexual partners. The latest update (12 March 2021) was endorsed by 1025 organizations across 102 countries ("Risk of sexual transmission of HIV from a person living with HIV who has an undetectable viral load – Messaging primer & consensus statement," 2021). This was confirmed by the PARTNER study which enrolled just over a 1000 serodiscordant couples and found that the risk of transmission was zero if the HIV positive partner taking ART had a VL of <200 copies/mL (Rodger et al., 2016).

Currently, there five classes of ART drugs that target various points of the life cycle of the virus. Prescription of more than a one class of ART drug, commonly referred to as highly active antiretroviral therapy (HAART) has been shown to optimally suppress the HIV VL and thereby improve overall outcomes in HIV positive patients by restoring immune system function and reducing the likelihood of acquiring opportunistic infections (Moore and Chaisson, 1999).

Currently available antiretroviral drugs can be divided into five classes based on the phase of the viral life cycle that they each inhibits (figure 5). To reduce the risk of developing drug resistance, ART agents are used in various combinations. In general, a typical treatment regimen includes two different nucleoside reverse-transcriptase inhibitors (NRTI) as the "backbone" and either a protease inhibitor (PI), a non-nucleoside reverse-transcriptase inhibitor (NNRTI), or an integrase inhibitor as the "base." (Kemnic and Gulick, 2021). Common drug toxicities and side-effects of commonly prescribed ART drugs are described in table 1.

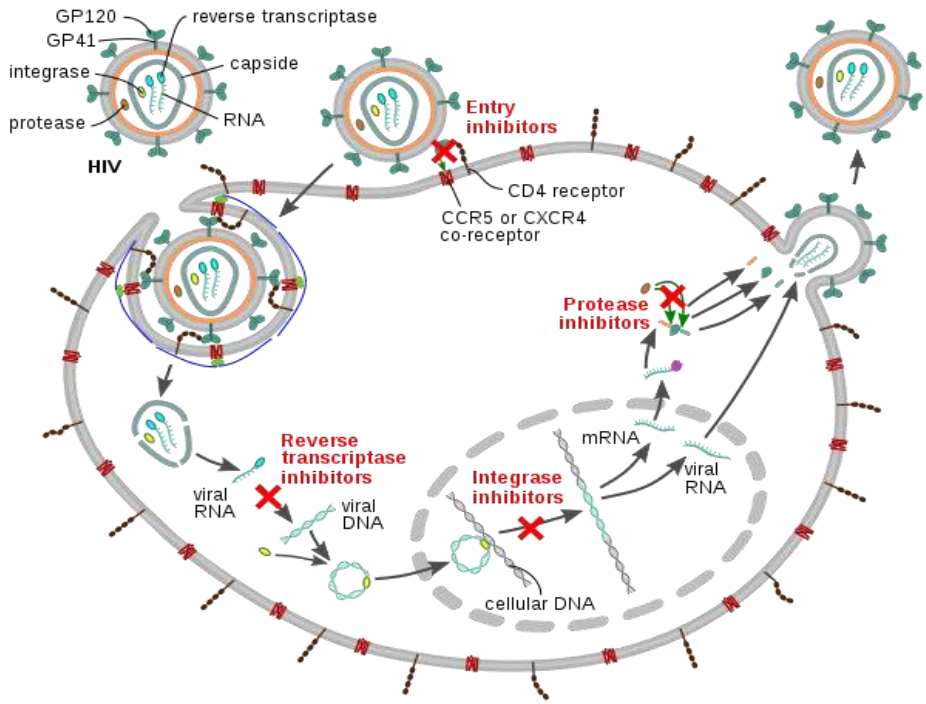


Figure 5: Mechanism of action of each of the classes of antiretrovirals
Image obtained from Splettstoesser T. HIV-drug-classes.svg. 2013. https://en.wikipedia.org/wiki/File:HIV-drug-classes.svg. Distributed under the terms of the Creative Commons Attribution 3.0 Unported (https://creativecommons.org/licenses/by/3.0/deed.en). No changes have been made to the image.

1.5.1 Entry inhibitors

This class of ART interferes with the binding, fusion, and entry of the virus into the host cell. It comprises two drugs, maraviroc, which targets the CCR5 co-receptor and enfuvirtide which acts by interfering with viral gp41 and thereby preventing infection of host cells (Bai et al., 2013; Lieberman-Blum et al., 2008).

1.5.2 Nucleoside and nucleotide reverse-transcriptase inhibitors

This class of drugs function as competitive substrate inhibitors that serve to inhibit the viral enzyme reverse transcriptase which is responsible for facilitating the transcription of HIV RNA viral protein into the host DNA. Nucleoside reverse-transcriptase inhibitors (NRTIs) function as chain terminators, hence, their incorporation into the DNA chain prevents assimilation of other nucleosides. NRTIs and nucleotide reverse-transcriptase inhibitors (NtRTIs) are both competitive substrate inhibitors. Examples of NRTIs include abacavir (ABC), didanosine (ddI), emtricitabine

(FTC), lamivudine (3TC), stavudine (d4T), zalcitabine (ddC) and zidovudine (AZT), while examples of NtRTIs include tenofovir (TDF) and adefovir (Das and Arnold, 2013).

Adverse effects of NRTIs include lactic acidosis, which is as a result of interference with host mitochondrial DNA synthesis and can be fatal. Other related adverse effects include hepatic steatosis, myopathy, peripheral neuropathy, and lipoatrophy (Lewis et al., 2003). However, the likelihood of mitochondrial dysfunction with commonly used first-line agents such as ABC, FTC, 3TC, and TDF is much lower than with ddI, D4T and others in this class (Johnson et al., 2001).

Table 1: Common drug toxicities and side-effects of commonly prescribed antiretroviral therapy drugs

Drug	Side-effects	Risk factors/ remarks
Abacavir (ABC)	Hypersensitivity reaction	Presence of HLA B*5701 gene
Atazanavir/r (ATZ/r)	Indirect hyperbilirubinemia	-Underlying hepatic disease -Hepatitis B or C virus co-infection -Concomitant use of hepatotoxic drugs
	Electrocardiographic abnormalities (PR interval prolongation)	-Pre-existing conduction disease -Concomitant use of other drugs that may prolong the PR interval
Dolutegravir (DTG)	Usually mild and self-limiting (headache, insomnia, central nervous system effects, gastrointestinal effects, increases risk of neural tube defects within the first six weeks of pregnancy	-Decreases tubular secretion of creatinine without affecting glomerular filtration, therefore a mild rise in creatinine is not a reason to stop DTG -Women of childbearing age must be counselled and offered contraception -Dose should be doubled in patients with rifampicin, carbamazepine, phenobarbital, and phenytoin co-administration -Use lower dose of metformin with DTG co-administration -Co-administration of polyvalent cations such as $Mg^{2+,}$ Fe^{2+}, Ca^{2+}, Al^{3+}, Zn^{2+} that are contained in antacids, sucralfate, multivitamin may also reduce levels by decreasing absorption
Efavirenz (EFV)	Psychiatric (abnormal dreams, depression, or mental confusion)	Depression or other mental disorder (previous or at baseline)

Emtricitabine (FTC)	Severe skin and hypersensitivity reactions, hyperpigmentation of palms and soles	Unknown risk factors
Lamivudine (3TC)	Headache, dry mouth	Unknown risk factors
Lopinavir/ ritonavir (LPV/r)	Diarrhoea, nausea, vomiting, dyslipidaemia, elevations in liver function tests, taste perversion	Oral solution contains alcohol, therefore avoid combining oral solution with metronidazole or disulfiram as this may cause a disulfiram-like reaction
Nevirapine (NVP)	Hepatotoxicity	-Underlying hepatic disease -Hepatitis B or C virus co-infection -Concomitant use of hepatotoxic drugs
	Convulsions	History of seizures
	Hypersensitivity reaction, Stevens- Johnson syndrome	Unknown risk factors
Ritonavir (r)	Nausea, vomiting, diarrhoea, abdominal pain, elevation of liver enzymes, fatigue, circumoral or peripheral numbness, taste perversion, hyperuricemia	-Oral solution contains alcohol, therefore avoid combining oral solution with metronidazole or disulfiram as this may cause a disulfiram-like reaction -Has significant interactions with many other medications
Tenofovir (TDF)	Flatulence, nausea, diarrhoea, abdominal discomfort, asthenia, acute renal insufficiency, Fanconi syndrome, chronic renal insufficiency	-Underlying renal dysfunction -In patients with HIV and hepatitis B co-infection, hepatitis may flare upon discontinuation -Gastrointestinal symptoms may be worse in lactose-intolerant patients as TDF is formulated with lactose
Zidovudine (AZT)	Anaemia, neutropenia, myopathy, lipoatrophy, or lipodystrophy	Baseline anaemia or neutropenia
	Lactic acidosis or severe hepatomegaly with steatosis	-BMI >25 (or body weight >75 kg) -Prolonged exposure to nucleoside analogues.

Adapted from:
1)2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates, 2019, https://sahivsoc.org/Files/2019 Abridged ART Guidelines 10 October 2019.pdf
2) National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents, and adults, 2015, http://www.sahivsoc.org/upload/documents/ART Guidelines 15052015.pdf

1.5.3 Non-nucleoside reverse-transcriptase inhibitors

Similar to NRTIs, non-nucleoside reverse-transcriptase inhibitors (NNRTI) also inhibit the viral enzyme reverse transcriptase. In contrast to NRTIs, they function as non-competitive inhibitors

of the enzyme by binding to an allosteric site of the enzyme. NNRTIs affect the handling of substrate (nucleotides) by reverse transcriptase by binding near the active site. First generation NNRTIs include the drugs nevirapine (NVP) and efavirenz (EFV), while second generation NNRTIs include the drugs etravirine (ETV) and rilpivirine (RPV). Suicidal ideation and other neuro-psychiatric side effects have been associated with the use of EFV, while severe hepatotoxicity has been associated with the use of nevirapine, especially in females with an elevated CD4 cell count (Usach et al., 2013).

1.5.4 Integrase inhibitors

This class of drugs which is also known as integrase nuclear strand transfer inhibitors (INSTIs), inhibits integration of viral DNA into host cell DNA by binding to the viral enzyme integrase. Examples of drugs in this class include raltegravir (RAL), dolutegravir (DTG), elvitegravir (EVG) and bictegravir (BIC) (Métifiot et al., 2013). This class of drugs are generally well tolerated with few adverse effects that include a rise in creatine kinase levels and myopathy (Lee and Carr, 2012).

1.5.5 Protease inhibitors

These drugs block the viral enzyme protease and thereby inhibit the cleavage of gag and gag/pol precursor proteins which is necessary for the production of mature virions prior to them budding from the host cell membrane. This results in the production of defective and predominantly non-infectious virions. Examples of drugs in this class include amprenavir (APV), atazanavir (ATV), darunavir (DRV), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), and ritonavir (r). Lipodystrophy and elevated serum triglycerides with a resultant increased risk of cardiovascular disease are common side effects that have been associated with the use of protease inhibitors. In addition, ritonavir which is a potent cytochrome P450 inhibitor increases the risk of drug-drug interactions (Walmsley, 2007; Wang et al., 2015).

1.5.6 Current ART treatment guidelines in South Africa

Sub-Saharan Africa bears the brunt of the global HIV pandemic, with South Africa housing the largest number of people with HIV than any other country in the world. As a result of political instability and government denial in the early days, the pandemic had reached catastrophic

proportions with escalating rates of infection, morbidity, and mortality towards the end of the 20th century and beginning of the 21st century. HIV first surfaced in SA in 1982. However, due to several reasons including high initial cost, lack of effective treatment regimens, changeover of political leadership, and government denial in the late 1990's and early 2000's, there was a significant lag in initiating free ART in the public sector during the early days of the SA pandemic. Hence, free ART drugs were only made available from April 2004 onward in the South African public sector after a lengthy battle between HIV activists and former President Thabo Mbeki together with the former Health Minister Dr Manto Tshabalala-Msimang, who questioned the link between HIV/ AIDS and ART effectiveness (Chichocki, 2020; Gonzalez, 2014).

In the 2004 National Antiretroviral Treatment Guidelines, only individuals with stage 4 disease and those with a CD4 cell count <200 cells/mm^3 were eligible to be initiated on HAART in the public sector. For the treatment of adults at that time and dependant on specific criteria, regimen 1 of HAART comprised of a combination of two drugs (d4T and 3TC) from the class NRTI's together with a single drug (EFV or NVP) from the class NNRTI, while regimen 2 for treatment failure comprised AZT, ddI and LPV/r ("National Antiretroviral Treatment Guidelines," 2004).

In the 2010 national ART guidelines, the eligibility criteria for initiation of ART was slightly adjusted. While general eligibility criteria for initiation remained the same at WHO stage 4 disease or CD4 cell count ≤200 cells/mm^3, additionally patients with comorbid tuberculosis (TB) and pregnant women were eligible for initiation of ART with a CD4 cell count ≤350 cells/mm^3, while all HIV positive patients with multidrug resistant (MDR)/ extensively drug resistant (XDR) TB irrespective of the CD4 cell count were also eligible to be initiated on ART. Pregnant women, patients with a CD4 cell count <100 cell/mm^3, patients with WHO stage IV clinical disease and with a CD4 cell count not yet available and patients with MDR/ XDR TB were deemed eligible for fast tracking and initiation of ART within two weeks of initial assessment. Due to high levels of serum triglycerides and cholesterol associated with thymidine analogue containing HAART such as d4T, changes were also made to the 1st line regimen where d4T was replaced with TDF for all new patients being initiated on ART and also in patients that were already on a d4T based regimen but were experiencing intolerable side effects to d4T. Among

patients with renal disease in whom TDF was contraindicated, d4T was switched to AZT. The guidelines also indicated that 3TC could be used interchangeably with FTC ("The South African Antiretroviral Treatment Guidelines 2010," 2010). A study showed that TDF was associated with a significant decrease in serum triglycerides and cholesterol compared to TDF (Milinkovic et al., 2007).

In the 2013 guidelines, criteria for the eligibility to start ART was updated in that irrespective of the WHO clinical stage, all patients with a CD4 cell count ≤350 cells/mm^3, all patients with any type of TB and all pregnant or breast-feeding women were eligible to be initiated on ART. Additionally, all patients with WHO stage 3 or 4 disease irrespective of the CD4 cell count were also eligible to be initiated on ART. Patients with cryptococcal meningitis or TB meningitis were also eligible to be initiated on ART four to six weeks after initiating specific therapy for these conditions. HIV-positive women who were pregnant or breast-feeding patients with a low CD4 cell count (<200 cells/mm^3), patients with Stage 4 disease irrespective of the CD4 cell count and patients with co-morbid TB and a CD4 cell count <50 cells/mm^3 were deemed eligible for fast tracking and initiation of ART within 7 days of initial assessment. The guidelines recommended using of a single tablet fixed drug combination (FDC) pill and mandatory switching of d4T to TDF in patients experiencing toxicity as well as patients at high risk of toxicity (high body mass index or pregnancy). The guidelines also recommended switching d4T to TDF in all other patients on a d4T based regimen provided they were virally suppressed and had a normal creatinine clearance, even if the d4T based regimen was well tolerated. The guidelines further recommended that TDF be replaced with AZT in patients in whom TDF was contraindicated (underlying renal disease or use of other nephrotoxic drugs). The prescription of d4T was only indicated if both TDF and AZT were contraindicated, while the prescription of ABC was only indicated when all three of TDF (renal toxicity), AZT (anaemia) and d4T (peripheral neuropathy) were contraindicated. The rest of the 1st line regimen (3TC or FTC and EFV or NVP) remained unchanged as compared to the previous guidelines. In the second line regimen (due to failure of the first line regimen), the NNRTI was replaced with lopinavir/ritonavir LPV/r. Where LPV is not tolerated due to diarrhoea or dyslipidaemia, ATV was recommended as a replacement ("The South African Antiretroviral Treatment Guidelines 2013," 2013).

The 2015 version of the recommended ART treatment was very similar to the 2013 guidelines, with additional guidelines for those that were hepatitis B virus co-infected. Importantly, criteria for the eligibility to initiate ART were further relaxed in that all patients with a CD4 cell count ≤500 cells/mm^3 were now eligible to be initiated on ART, with those with a CD4 cell count ≤350 cells/mm^3 to be fast-tracked for initiation. Patients with hepatitis B virus co-infection were also eligible to be initiated on ART, irrespective of their CD4 cell count. In addition, the guidelines also recommended that in the absence of contraindications, ART must be initiated within two weeks of the CD4 cell count being measured ("National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the management of HIV in children, adolescents and adults," 2015).

In September 2016, the minister of health announced that ART was freely available to all South Africans living with HIV, irrespective of their CD4 cell count or stage of disease. The most recent South African HIV clinical guidelines were published in October 2019, and predominantly focused on replacing EFV with DTG for all HIV-positive patients >10 years and weighing ≥35 kg, in a new fixed-dose combination. Advantages of DTG include minimal side effects, achievement of rapid viral suppression, a high genetic barrier to resistance and few drug interactions including no interactions with hormonal contraception. Although DTG has a good side effect profile, it may be associated with weight gain and may be associated with a slightly higher risk of neural tube defects (NTDs), hence it is recommended that women of childbearing age should be counselled in this regard and offered contraception. With regards to drug interactions, rifampicin, carbamazepine, phenobarbital, and phenytoin co-administration decreases the levels of DTG, hence the dose should be doubled to a twice daily dose instead of a single dose. DTG also increases metformin levels, hence lower doses are recommended when this is prescribed. Co-administration of polyvalent cations such as Mg^{2+}, Fe^{2+}, Ca^{2+}, Al^{3+}, Zn^{2+} that are contained in antacids, sucralfate, multivitamin, and other nutritional supplements can also reduce DTG levels by decreasing its absorption. The guidelines provide detailed recommendation for switching patients to DTG. Due to their high genetic barrier, resistance to DTG and PIs develop very slowly. An elevated VL in patients on DTG or LPV/r is therefore more likely to be related to suboptimal adherence. Therefore, patients on these drugs presenting with ART failure should be extensively counselled and continued on these drugs for at least two

years prior to considering a switch to a second or third-line regimen ("2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates," 2019).

1.6 Non-adherence to antiretroviral therapy

The use of ART in PLWH has been associated with an improvement in health related quality of life and an overall reduction in the transmission of HIV (Albert et al., 2014; Gakhar et al., 2013), whereas suboptimal adherence has been associated with a reduction in the rates of viral suppression and an increase in the rates of viral resistance, opportunistic infections, progression to AIDS and mortality (Arnsten et al., 2001; Bangsberg et al., 2001; Low et al., 2016; Mannheimer et al., 2002; Maphula et al., 2020). Malignancies, cardiovascular diseases and other non-HIV related conditions have also been reported to be higher among ART non-adherent persons (El-Sadr et al., 2006; Silverberg et al., 2007).

ART non-adherence in the context of HIV refers to the failure to utilize ART medication as prescribed. Various methods of determining ART non-adherence have been described, including patient self-reporting, conducting pill counts, monitoring pharmacy records, utilizing electronic medication monitoring devices and conducting laboratory tests to monitor for virological (HIV VL) or immunological (CD4 cell count) failure (Turner, 2002). Due to its ease of use, patient self-reporting is the most widely used method to determine ART adherence (Berg and Arnsten, 2006), however, it has a tendency to overestimate ART adherence (Arnsten et al., 2001). One of the most commonly used self-reporting methods is the AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ) that comprises four questions that can be easily recalled: 1) have you missed your antiretroviral therapy pills yesterday; 2) have you missed your antiretroviral therapy pills the day before yesterday; 3) have you missed your antiretroviral therapy pills the past weekend; and 4) have you missed your antiretroviral therapy pills in the last two weeks (Chesney et al., 2000).

To achieve optimal viral suppression, ART adherence should be maintained above 90-95% (Bangsberg et al., 2001; Paterson et al., 2000; Turner, 2002). ART adherence rates and reasons for adherence or non-adherence are influenced by various factors that vary from region to region.

In 2014, the UNAIDS as part of their 90-90-90 treatment goals to help end the HIV pandemic had set a target for 90% of persons diagnosed with HIV to be on sustained ART by the year 2020 ("90-90-90 An ambitious treatment target to help end the AIDS epidemic," 2014).

Results of a meta-analysis published in 2011 that comprised 84 studies with 33 199 pooled patients indicated that the global overall rate of ART adherence was 62% (Ortego et al., 2011). In a recent study that was conducted in Nepal, the overall ART adherence in the six months prior was 87.4%, with use of a wristwatch or mobile phone reminder. Female sex, not drinking alcohol, duration of HIV infection of more than 3 years, collecting their ART personally and a lack of medication side effects were associated with a higher likelihood of medication adherence (Neupane et al., 2019).

In a study that was conducted in Kenya, non-adherence was reported in 51.1% of participants in the 30 days before collection of data with the main reasons being forgetfulness (43.9%); prolonged waiting time (41.1%), long queues (25.5%), long distance to the facility (21%), work (18.4%) and lack of family support (14.8%) (Kithinji and Wankuru, 2019). In a qualitative study that was conducted in the Western Cape province of South Africa where 18 non-adherent patients were subjected to in-depth interviews; economic barriers such as poverty, unemployment, lack of money for transport and lack of food were reported as the predominant reasons for ART non-adherence. The study also reported that some patients deliberately stopped taking their ART to induce a drop in their CD4 cell count and thereby precipitate an acute illness so as to be unable to work and hence qualify to receive a disability grant. Other reported reasons included stigma and discrimination, fear of been seen by someone they know while collecting their ART, poor treatment literacy, medication side effects, feeling better, alcohol use, smoking, emotional distress, forgetfulness and alternative forms of therapy (traditional medicines) (Azia et al., 2016). Another recent study conducted in Korea reported that subjects who were prescribed a single-tablet regimen were 5.1 times more adherent with their ART than patients who were taking multiple pills. Non-adherence was also more likely in those with an initial viral load ≥500 000 copies/ml (Oh and Han, 2021).

Differences in race and ethnicity have also been shown to influence ART adherence rates. In a USA based study, where the authors subjected the data to logistic regression while controlling for age, gender, income, education, site, depression and substance abuse; ART adherence was found to be significantly lower among African Americans compared to Latinos (OR 0.72, p=0.004) and Whites (OR 0.60, p<0.001) (Simoni et al., 2012). However, the same may not apply to sub-Saharan Africa.

1.7 Predictors of poor outcomes among HIV-positive patients

Determining factors that are associated with poor outcomes such as prolonged hospital stay and mortality among HIV-positive patients may be of value in guiding clinical decision making, directing the appropriate use of resources, and influencing patient disposition. It may also be useful in developing an outcome prediction tool for use in HIV-positive patients presenting with an acute illness.

Although multiple studies have reported on the predictive value of various parameters in HIV-positive patients, most of these studies only reported on a few variables and most studies were predominantly conducted in outpatient settings and not hospitalised patients. A mixed method review study identified various factors including late presentation, lack of in-hospital testing for HIV, poor overall laboratory capacity, delays in ART initiation, and loss to follow-up as factors that were associated with preventable in-hospital mortality (Wajanga et al., 2014). Other factors influencing ART adherence are discussed below.

1.7.1 Demographic characteristics

Age

In general, increasing age has been associated with higher rates of in-hospital mortality (Rosenthal et al., 2002). This is likely due to the presence of concurrent multiple comorbid illnesses such as hypertension, diabetes mellitus, hypercholesterolaemia, malignancy, etc., that are more prevalent with increasing age (Divo et al., 2014). HIV-positive patients who are virally suppressed have been shown to have higher rates of cardiovascular, neurological, renal and oncological diseases than the general population (Wing, 2016). A multicentre study that included data from 12 078 hospitalized HIV-positive patients across 43 hospitals in Portugal over a three-

year period, reported that each additional year increase in age was associated with a 1.3% higher risk of in-hospital mortality (Dias et al., 2009). Surprisingly, a study conducted in Louisiana, USA reported that age was not a significant predictor of prolonged hospital length of stay (LOS) (Santella et al., 2010).

Sex

Although females make up the majority of HIV infections in sub-Saharan Africa, ("UNAIDS Data 2020," 2020) studies have reported higher rates of mortality among men with HIV (Angdembe et al., 2019; Dias et al., 2009; Rubaihayo et al., 2015). Data collected from 2000-2011 in rural KwaZulu-Natal, South African showed that man were 25% more likely to die from HIV than females (Bärnighausen et al., 2014). Reasons for poorer outcomes among men are that men are less likely to test for HIV, are less likely to start ART after testing positive, usually start ART late, have poorer adherence rates and are more likely to be lost to follow-up (Hawkins et al., 2011; Kranzer et al., 2010; Muula et al., 2007; Ochieng-Ooko et al., 2010; Venkatesh et al., 2011).

Marital status

Being married has been associated with better survival from various illnesses (Chandra et al., 1983; C. C. Yang et al., 2019). The same holds true for HIV. A study that analysed data from the US National Longitudinal Mortality Study reported that compared to PLWH that were married, those that were divorced or separated and those that were never married were 4.3 times (adjusted relative risk (aRR) 4.32, 95% CI 2.98-6.27) and 13 times more likely to die from HIV-related illnesses (aRR 13.09, 95% CI 9.65-17.76) respectively (Kposowa, 2013). A recent study that was conducted in Georgia showed that compared to HIV-positive individuals that were married, widowed patients were 8.25 times (OR 8.25, 95% CI 3.10-21.94, $p < 0.05$) more likely to die from HIV-related illnesses, while there were no significant differences between the married versus divorced as well as between the married versus never married groups (Nkwanwoh, 2021).

Education

A recently published study that was conducted in Ghana and included 2 660 women between the ages of 15-49 years, found that HIV testing was higher among women with secondary school or

higher education compared to those with no education (89.5% vs 76.8%) (Sambah et al., 2020). Another similar study that was conducted in Zambia and comprised 15 388 women aged between 15-49 years also concluded that educational attainment was a strong predictor of HIV testing (Muyunda et al., 2018). A collaborative cohort study that comprised 24 069 HIV-positive patients across eight countries in Europe concluded that lower educational levels in HIV-positive patients was associated with a poorer response to ART as well as higher mortality (del Amo et al., 2017).

Nationality

It is uncertain whether foreign nationals are at higher risk of HIV-related morbidity and mortality. A longitudinal study that investigated within-country migration and maternal mortality among HIV-positive postpartum women in rural South Africa, found that the hazard of mortality was close to three times higher (hazard ratio (HR) 2.74; 95% CI 1.01–7.40, p = 0.047) among HIV-positive women who migrated (Kim et al., 2020).

1.7.2 Vital signs

Vital signs such as blood pressure, heart rate, respiratory rate, oxygen saturation etc. can be easily determined within minutes of a patient's presentation to the ED. These convey information to the clinician with regards to the severity of the patient's illness, underlying physiological derangement and the need for life-saving interventions (Lockwood et al., 2004). In a retrospective study that was conducted in Spain and looked at mortality predictors in septic HIV-positive patients, tachycardia, hypotension, hypercapnia within the first 24 hours of ICU admission was significantly associated with ICU mortality (Vidal-Cortés et al., 2013). Another study identified hypotension and hypoxaemia as predictors of mortality at initial presentation of HIV-positive patients with Pneumocystis jirovecii pneumonia (Wang et al., 2011). Yet another study comprising 347 HIV-positive patients from Ethiopia with neurological manifestations, reported that a derangement in the level of consciousness and seizures were significant predictors of mortality (Berhe et al., 2012).

1.7.3 Laboratory markers

CD4 cell count and HIV viral load

Various studies have reported a low CD4 cell count at initiation of ART as a predictor of mortality in HIV-positive patients (Bisson et al., 2008; Lawn et al., 2008; Sieleunou et al., 2009). In another study, patients with a low CD4 cell count were more likely to require hospitalization (Krentz et al., 2006). A high HIV VL has also been associated with an increase in mortality. A study showed that inadequate suppression of the HIV VL six months post initiation of ART was associated with a substantial risk of 10-year all-cause mortality (Lee et al., 2017). In another study that was conducted in patients on ART, the CD4 cell count, but not the HIV VL was associated with mortality (Mijch et al., 2001).

Anaemia, leukopenia and thrombocytopaenia

Anaemia as a predictor of poor outcomes in patients with HIV has been described in a number of studies (Chalamilla et al., 2012; Cuong et al., 2012; Gupta et al., 2011; Poka-Mayap et al., 2013). It has been associated with decreased survival, and more rapid progression of disease (Volberding et al., 2004). In the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project that was conducted in the USA and comprised 32 867 subjects, the median survival was significantly shorter in HIV-positive persons with an anaemia (haemoglobin <10 g/dL) irrespective of the CD4 cell count. (Sullivan et al., 1998). The EuroSIDA study that comprised 6 725 patients from across Europe showed that every 1 g/dL decrease in haemoglobin was independently associated with a 57% increase in mortality (Mocroft et al., 1999). In a cohort study that included 1 350 adults that had been initiated on ART across 27 clinics in South Africa, the adjusted hazard ratio (aHR) for mortality with a haemoglobin <8 g/dL and 8.1-9.9 g/dL was 4.99 and 3.05 times higher, respectively (Russell et al., 2010). Although leukopenia and thrombocytopaenia have not been as widely studied as anaemia for its outcome predictive value in HIV-positive patients, a study that enrolled 320 treatment-naïve adults at ART initiation that were followed for a median duration of 10.9 months reported that both thrombocytopenia (aHR 2.30) and lymphopenia (aHR 1.72) were independent predictors of mortality (Johannessen et al., 2008).

Renal dysfunction

Rates of renal dysfunction among acutely ill HIV-positive patients are reported to be higher than the general population. Various studies have reported rates that range between 2.9% and 18%

(Franceschini et al., 2005; Lopes et al., 2011; Wyatt et al., 2006), with the rates being higher among those with a lower CD4 cell count and higher HIV VL (Franceschini et al., 2005). Even in the post-ART era, the incidence of renal dysfunction among PLWH still remains high (Wyatt et al., 2006).

Elevated C-reactive protein

In a multicentre study that comprised 513 HIV-positive men, the degree of CRP elevation was associated with HIV disease progression that was independent of the CD4 cell count and HIV VL (Lau, 2006). In another study, after adjusting for age, body mass index, albumin, CD4 cell count and HIV VL, CRP was found to be a predictor of mortality with the risk varying from 3.4 to 13.6 times higher and dependant on the degree of CRP elevation (Feldman et al., 2003). A study conducted in Tanzania found that a high maternal CRP independently predicted maternal as well as child mortality (Drain et al., 2007).

Hyperlactatemia

Hyperlactataemia in HIV-positive patients was more common during the period when the older generation NRTIs such as d4T and ddI were in common uses, however, with the use of safer ART regimens, the incidence has significantly declined over the past few years ("HIV and Lactic Acidosis," 2020). There are however other causes of hyperlactataemia in patients with HIV. In a small study that included 37 HIV-positive patients with hyperlactataemia, the overall mortality rate was 45.9% with sepsis (48.7%), pancreatitis (13.5%), liver failure (8.1%) and multiorgan failure (8.1%) being reported as the most common causes of hyperlactataemia (Tantisiriwat et al., 2001). In the general population, hyperlactatemia has been shown to be an independent predictor of mortality in acutely ill patients presenting to hospital (Khosravani et al., 2009; Stacpoole et al., 1994). Hence, lactate levels may be useful as a predictor of poor outcomes in acutely ill HIV-positive patients requiring hospital care.

Hypoalbuminemia

Hypoalbuminemia has also been shown to predict mortality in HIV-positive patients. In a study comprising of 2 056 HIV-infected women at various stages of HIV disease, the aHR for mortality was 3.1 times higher ($p < 0.01$) in patients with an albumin <35 g/L (Feldman et al.,

2000). In another study, the risk of mortality was three times higher in HIV-positive patients with an albumin <25 g/L (Lang et al., 2013). Another study that included 2 145 adults, patients with an albumin <35 g/L had a hazard ratio of death of 4.52 times ($p < 0.001$) compared to those with an albumin ≥ 35 g/L (Sudfeld et al., 2013).

1.7.4 Presenting diagnosis

In a study, the presence of an AIDS defining illness was strongly correlated with requiring hospitalization ($p <0.01$) (Krentz et al., 2006). A study that was conducted in Portugal showed that HIV-positive patients co-infected with tuberculosis had an overall longer length of hospital admission (Augusto et al., 2019). Co-infection with TB has also been significantly associated with mortality among HIV-positive patients (Amuron et al., 2011; Ghate et al., 2011; Kigozi et al., 2009). In a study, the risk of death in HIV-positive patients that were co-infected with TB was double that of HIV-negative patients without TB (Suchindran et al., 2009). Another study showed that bacterial pneumonia was associated with a 43% higher risk of in-hospital mortality (Dias et al., 2009).

A study reported that HIV clinical stage 3 (aHR) 1.67) or 4 (aHR 2.21) disease was predictive of mortality (Angdembe et al., 2019). The presence of an AIDS defining illness has also been shown to be a predictor of prolonged hospitalization (Santella et al., 2010). A systematic review that included 17 studies from Ethiopia and comprised 19 321 pooled HIV-positive patients on ART reported that stage 3 and 4 disease was significantly associated with higher mortality (aHR 1.4-11.2) (Biset Ayalew, 2017). Other studies reported that bacterial meningitis and cryptococcal meningitis were also associated with a significantly higher likelihood of in-hospital mortality (Jarvis et al., 2014; Wall et al., 2013).

1.7.5 Intensive care unit admission

In a study that retrospectively reviewed the data of patients that were admitted to a tertiary level ICU in Johannesburg, South Africa in 2017, ICU mortality was significantly higher among HIV-positive patients compared to HIV-negative patients that were admitted over the same time period (68/204 [33.3%] vs 131/699 [18.7%]; $p =0.00001$). In addition, a further 34 patients (16.7%) demised in the general ward after being discharged from the ICU and prior to hospital

discharge, giving an overall in-hospital mortality rate of 50% among HIV-positive patients admitted to the ICU. On multivariate analysis of the data, a non-sepsis related illness, requirement for inotrope/ vasopressor support and requirement for mechanical ventilation were proven to be predictors of ICU mortality (Maphula et al., 2020). In another retrospective study that was conducted in Spain and included data of patients that were admitted to the ICU between 2005 – 2010, the overall mortality at 90 days among patients that were admitted to the ICU was significantly higher in HIV-positive patients compared to HIV-negative patients (80.9% vs 58.9%; $p < 0.001$) (Medrano et al., 2014).

1.8 Outcome prediction models

Predictive modelling in clinical medicine is aimed at predicting specific outcomes of interest by combining multiple patient characteristics or parameters to estimate the likelihood that a certain outcome is present or will ensue. Selected parameters are generally allocated specific weightings that are summed-up to achieve a total score that is predictive of specified outcomes. Predictive models serve to complement clinician expertise and experience by providing objective data relating to disease severity, treatment success etc., and thereby reduce the risk of clinician bias during decision making and resource allocation (Shipe et al., 2019; Shmueli, 2010).

There are several steps involved in developing and validating a prediction model prior to its implementation in clinical practice. Defining the purpose of the model including the outcome of interest (e.g., death, cancer diagnosis, ICU admission), the specific target population and setting (e.g., in-patient versus out-patient setting) is the first step. The defined outcome should preferably be practical, clinically relevant and reproducible across the spectrum of disease (Shipe et al., 2019; Steyerberg, 2020).

Careful identification and selection of parameters or predictor variables is the next important step in the development of the model. Predictor variables are usually selected after subjecting data from the target population to statistical analysis (e.g., logistic regression analysis) or machine learning techniques such as artificial neural networks, decision trees, support vector machines, Bayesian networks etc., to determine which parameters are of value in predicting the outcome of interest. However, review of the literature and opinion of clinical experts may also influence

variable selection. Examples of candidate predictor variables include demographic characteristics such as age, sex etc., findings from patient history and examination, presence of comorbid illnesses, laboratory findings and radiology results. Predictors must be clearly defined and specified (e.g., the range for categorical variables such as age or the cut-off levels for continuous variables). Limiting the number of predictor variables in the final model will increase the likelihood that the model will be implemented in routine clinical practice. This can be achieved by combining similar predictors (e.g., coronary artery disease and cerebrovascular accident can be combined as "cardiovascular risk"), excluding predictors that are highly correlated (e.g., not including both urea and creatinine) and omitting variables that are not routinely measured (e.g., specific findings on magnetic resonance imaging scanning). Each of the included parameters are thereafter allocated weightings that are mostly based on how strongly each contributes to the outcome of interest after being subjected to logistic regression analysis. The next step is to assess the performance of the model. There are several ways of assessing this such as 1) correlating the total score achieved against the actual rates of the outcome of interest, 2) determining if there is a positive relationship between the score achieved and the predicted probability of the outcome of interest, 3) assessing discrimination and 4) assessing calibration (Shipe et al., 2019; Steyerberg, 2020).

Discrimination refers to the ability of a model to distinguish between patients with the outcome of interest (e.g., mortality) and those without the outcome of interest. It is measured by determining the area under the receiver operating characteristic curve (AUROC), which plots the sensitivity (true positive rate) against 1 – specificity (false positive rate) (Laher et al., 2017; Obuchowski, 2003). Calibration refers to the agreement between observed outcomes and expected outcomes (predictions) (Alba et al., 2017). For example, if a 20% risk of mortality is predicted, the observed frequency of mortality should be approximately 20 of 100 patients. Calibration can be measured using several tests such as Spiegelhalter's z test, the Hosmer-Lemeshow test, Cox intercept and slope and maximum calibration error (Huang et al., 2020).

The model should then be subjected to internal validation. Internal validity is the extent to which one can be confident that a cause-and-effect relationship is not due to other factors and is performed on the same study sample that was used to develop the model. A few methods of

performing internal validation have been described. In the split-sample approach, the data is randomly split into two parts, with one part being used to develop the model and the other to measure its performance (internal validation). The cross-validation approach is another method of internal validation which is an extension of the split-validation approach. Here, the model is developed on a specified randomly chosen fraction of the sample and validated on the remaining fraction of the sample (e.g., 30% and 70%). The procedure may be repeated several times using the same fraction but on different randomly chosen samples. The average is then regarded as an estimate of the model's performance. The bootstrap method is regarded as one of the most effective methods of validating a prediction model and relies on computer-intensive resampling techniques. It involves a process of random sampling with replacement from an original dataset for use in obtaining statistical inference (Efron, 1983; Efron and Tibshirani, 1997; Steyerberg et al., 2001). Typically, the model's performance (discrimination and calibration) is estimated in over 100 smaller samples drawn from the original samples, and the average calculated to validate the model. In a study that compared three different methods of internal validation, the authors concluded that performance of both the split-sample and cross-validation methods were suboptimal compared to the bootstrap method (Steyerberg et al., 2001).

External validity is determined by subjecting the model to a different sample to the one that was used to develop the model. It seeks to determine whether the model will perform adequately across varying populations, times, and settings. This step is usually performed after findings of the internal validation are published. Finally, the clinical impact or usefulness of the model should be assessed (Moons et al., 2012).

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CHAPTER 2: STUDY AIM AND OBJECTIVES

This study aimed to explore the clinical presentation and characteristics including factors influencing ART non-adherence, hospital length of stay and in-hospital mortality and to develop and validate an in-hospital mortality prediction model in HIV-positive patients presenting to the ED. To achieve these, the following objectives were pursued:

Objective 1: To describe the patterns of presentation of HIV-positive patients to the CMJAH ED.

Outcome: The methodology, results and discussion, limitations and conclusion are described in Chapter 3 (Publication 1).

Brief summary of findings: Of the 1 224 participants that were enrolled, 673 (55.0%) were male, 937 (76.6%) were married, HIV was newly diagnosed in 212 (17.3%) patients, 761 (75.2%) of those who were previously diagnosed with HIV were on ART, 245 (32.2%) of those on ART reported non-adherence, 276 (22.5%) had bacterial pneumonia, 244 (19.9%) had tuberculosis (TB), 86 (7.0%) had gastroenteritis, 205 (16.7%) required intensive care unit admission, 381 (31.1%) required hospital admission for ≥7 days, 166 (13.6%) died, CD4 cell count was <100 cell/mm^3 in 527 (47.6%), HIV VL was >1000 copies/mL in 619 (59.0%), haemoglobin was <11 g/dL in 636 (56.3%), white cell count was <4.0 x 10^9/L in 170 (15.1%), platelet count was <150 x 10^9/L in 223 (19.9%), urea was >10 mmol/L in 277 (25.9%), creatinine was >120 μmol/L in 294 (29.3%), CRP was >100 mg/L in 516 (48.7%), lactate was >2 mmol/L in 470 (42.0%), albumin was <35 g/L in 633 (60.8%) and alanine transaminase was >100 mmol/L in 109 (10.6%).

Objective 2: To explore ART non-adherence and its associations and to determine the reasons for non-adherence among HIV positive patients presenting to the CMJAH ED.

Outcome: The methodology, results and discussion, limitations and conclusion are described in Chapter 4 (Publication 2).

Brief summary of findings: Of the 1 224 participants that were enrolled, 761 (75.2%) were on ART at the time of ED presentation. Of these, 245 (32.2%) were non-adherent as per the ACTG-AQ. Participants not yet on ART prior to ED presentation demonstrated a significantly higher in-hospital mortality than participants on ART (OR 1.69, 95% CI 1.21-2.34, p =0.002). Younger age, male sex, CD4 <100 cell/mm^3, lack of viral suppression, a high NEWS-2 score (≥7 points), and length of hospital stay ≥7 days were significantly associated with ART non-adherence (p <0.05). Forgetfulness (13.9%), lack of social support, depression/ stress/ mental illness, and lack of transport money to collect medications (9.9% each) were the commonest reasons given for ART non-adherence.

Objective 3: To identify predictors of prolonged hospital stay among HIV-positive patients presenting to the CMJAH ED.

Outcome: The methodology, results and discussion, limitations and conclusion are described in Chapter 5 (Publication 3).

Brief summary of findings: Among the 1 224 participants that were enrolled, the median (IQR) LOS was 4.9 (3.5-8.0) days, while the mean (SD) LOS was 6.6 (8.3) days. On multivariate analysis of the data, haemoglobin <11 g/dL (OR 1.37, p =0.032), GCS <15 (OR 1.80, p =0.001), creatinine >120 μmol/L (OR 1.85, p =0.000), cryptococcal meningitis (OR 2.45, p =0.015) and bacterial meningitis (OR 4.83, p =0.002) were significantly associated with a higher likelihood of LOS ≥7 days, while bacterial pneumonia (OR 0.35, p =0.000) and acute gastroenteritis (OR 0.40, p =0.025) were significantly associated with a lower likelihood of LOS ≥7 days.

Objective 4: To identify predictors of in-hospital mortality among HIV-positive patients presenting to the CMJAH ED.

Outcome: The methodology, results and discussion, limitations and conclusion are described in Chapter 6 (Publication 4).

Brief summary of findings: Of a total of 1 224 participants that were enrolled, the in-hospital mortality was 13.6% (n=166). On multivariate analysis, respiratory rate >20 breaths/min (OR 1.90, p =0.012), creatinine >120 μmol/L (OR 1.97, p =0.006), oxygen saturation <90% (OR 2.09, p =0.011), white cell count <4.0 x 10^9/L (OR 2.09, p =0.008), ART non-adherence or not yet on ART (OR 2.39, p =0.012), GCS <15 (OR 2.53, p =0.000), albumin <35 g/L (OR 2.61, p =0.002), lactate >2 mmol/L (OR 4.83, p =0.000) and cryptococcal meningitis (OR 6.78, p =0.000) were significantly associated with in-hospital mortality.

Objective 5: To develop and internally validate the HIV In-hospital Mortality Prediction (HIV-IMP) model.

Outcome: The methodology, results and discussion, limitations and conclusion are described in Chapter 7 (Publication 5).

Brief summary of findings: The overall in-hospital mortality rate was 13.6% (n=166). Eight predictors were included in the final model: ART non-adherence or not yet on ART, GCS <15, respiratory rate >20 breaths per minute, oxygen saturation <90%, white cell count <4 x 10^9/L, creatinine >120 μmol/L, lactate >2 mmol/L and albumin <35 g/L. After internal validation, the model maintained good discrimination (AUROC 0.83, 95% confidence interval (CI) 0.78 – 0.88) and calibration (Hosmer-Lemeshow χ^2 2.26, p = 0.895).

CHAPTER 3: ARTICLE 1

The manuscript was published in the journal *Southern African Journal of HIV Medicine* on 29 January 2021: doi:10.4102/sajhivmed.v22i1.1177. The journal is indexed in PubMed, Web of Science (Impact Factor 2.50) and Scopus (CiteScore 1.3).

Profile of presentation of HIV-positive patients to an emergency department in Johannesburg, South Africa

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3.1 Abstract

Background: Despite improved availability and better access to antiretroviral therapy (ART), approximately 36% of human immunodeficiency virus (HIV)-positive South Africans are still not virally suppressed.
Objectives: The aim of this study was to describe the patterns of presentation of HIV-positive patients to a major central hospital emergency department (ED).

Methods: In this prospectively designed study, consecutive HIV-positive patients presenting to the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) adult ED were enrolled between 07 July 2017 and 18 October 2018.
Results: A total of 1 224 participants were enrolled. Human immunodeficiency virus was newly diagnosed in 212 (17.3%) patients, 761 (75.2%) were on ART, 245 (32.2%) reported ART non-adherence, 276 (22.5%) had bacterial pneumonia, 244 (19.9%) had tuberculosis (TB), 86 (7.0%) had gastroenteritis, 205 (16.7%) required intensive care unit admission, 381 (31.1%) were admitted for ≥7 days and 166 (13.6%) died. With regard to laboratory parameters, CD4 cell count was <100 cell/mm3 in 527 (47.6%) patients, the viral load (VL) was >1000 copies/mL in 619 (59.0%), haemoglobin was <11 g/dL in 636 (56.3%), creatinine was >120 μmol/L in 294 (29.3%), lactate was >2 mmol/L in 470 (42.0%) and albumin was <35 g/L in 633 (60.8%).
Conclusion: Human immunodeficiency virus-positive patients presenting to the CMJAH ED demonstrated a high prevalence of opportunistic infections, required a prolonged hospital stay and had high mortality rates. There is a need to improve the quality of ART services and accessibility to care.

Keywords
HIV; emergency department; ART non-adherence; CD4 cell count; HIV viral load; opportunistic infections; hospital admission; mortality.

3.2 Introduction

Human immunodeficiency virus (HIV) infection is an epidemic, which has affected approximately 38 million people worldwide. In 2019, 1.7 million new infections and 690 000 HIV-related deaths were recorded ("UNAIDS Data 2020," 2020). Two-thirds of the global population of persons living with HIV (PLWH) are in sub-Saharan Africa (SSA). South Africa (SA) contributes approximately 7.5 million to the global number, that is, more than twice that of any other country worldwide ("List of countries by HIV/AIDS adult prevalence rate," 2020).

The availability of antiretroviral therapy (ART) globally has reduced HIV-associated morbidity and mortality rates (Cornell et al., 2010; Zhu et al., 2013). Indeed, the life expectancy of PLWH in some regions is now comparable to that of the general population (Cornell et al., 2010; Jaggy

et al., 2003). Although there has been a significant increase in the global number of PLWH on ART in recent years ("UNAIDS Global Factsheets 2019," 2020), the burden of HIV-related illness is still substantial (Mitiku et al., 2015), especially amongst those who are newly diagnosed, ART-naive and those who were recently initiated on ART (Matoga et al., 2018). Other factors contributing to poor HIV-related outcomes include non-adherence to ART, treatment resistance and severe immune deficiency (low CD4 cell counts) at the time of presentation (Bangsberg et al., 2001). Furthermore, loss to follow-up (LTFU) remains a problem despite growth in the numbers starting on ART (Budgell et al., 2015; Cornell et al., 2010).

Emergency departments (EDs) are frequently the first 'port-of-call' for PLWH who experience an acute deterioration in health. Despite free access to ART in SA's public health system (Cullinan, 2016), recent data confirm that approximately 30% of eligible persons are not yet on ART, and of those on ART, 36% are not virally suppressed ("UNAIDS Data 2020," 2020). Although these figures have improved since the inception of the ART roll-out in 2004 ("UNAIDS Data 2019," 2019), admission with acute HIV-related illness is still high. These figures fall short of the 2020/30 Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 targets ("90-90-90 An ambitious treatment target to help end the AIDS epidemic," 2014). The country's healthcare service and in particular its EDs depict an early barometer of progress in achieving these goals.

In this study, we describe the profile of presentation of acutely ill PLWH to the ED of a large tertiary hospital. We also describe demographic characteristics, HIV-related history, vital signs, routine laboratory parameters, presenting diagnosis, patient disposition and outcomes.

3.3 Methods

This study was conducted in the adult medical-ED of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), a 1088-bed tertiary-level academic hospital affiliated to the University of the Witwatersrand. The adult medical ED manages all non-trauma patients who, on arrival, are triaged as 'emergent' (red), 'very urgent' (orange), 'urgent' (yellow) and 'routine' (green) based on specific criteria as defined by the SA Triage Scale (Bruijns et al., 2008). In general, patients who are triaged as 'routine' (green) are referred to a lower-level facility for

further management. In addition, patients not residing within the drainage area of the CMJAH, and who are transportation stable, are referred to an appropriate facility closer to the patient's residence.

Before the commencement of data collection, informal training pertaining to the methodology and principles of data collection from medical charts was undertaken by the primary investigator. Furthermore, all doctors employed in the ED were briefed regarding the aims, objectives, and design of the study. Doctors were thereafter requested to inform the primary investigator of all HIV-positive patients managed in the ED. Written informed consent for study participation was obtained by the primary investigator or the doctor on shift. If participants were unable to grant consent (e.g., decreased level of consciousness), consent was obtained from the next of kin/legal guardian and later re-obtained from the participant after his or her mental condition had improved. Human immunodeficiency virus-negative patients, HIV-unknown patients not consenting to HIV testing and patients not consenting to participate in the study were excluded from the study. Emergency department registers were also reviewed daily in an effort to identify potential participants who were missed by the ED doctors.

The four-question AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ) was used in order to determine non-adherence to ART (Chesney et al., 2000). The questionnaire was administered to all participants prescribed ART at any time in the past.

Data were extracted from the patient's hospital records by the primary investigator and entered into an anonymised and standardised data collection form. Additional information relevant to the study but not found in the patient's hospital records was directly obtained from the participant, the participant's laboratory records or the participant's next of kin/legal guardian where applicable. Only where the next of kin/legal guardian indicated that they were aware of the participant's HIV status, they were questioned regarding relevant HIV-history such as treatment adherence. Data from hospital records were recorded daily for the entire duration of hospital stay until data collection was completed. Inter-rater reliability was assessed by an independent researcher experienced in the methods of data collection and blinded to the study aims and

objectives. Data extracted from a random sample of 43 medical charts were compared with those extracted by the primary investigator.

Data relevant to this study included demographic details, HIV status, prior ART history including non-adherence, vital signs including the Glasgow Coma Scale (GCS) score, respiratory rate, systolic blood pressure, oxygen saturation, heart rate and temperature, baseline laboratory findings at the time of the current presentation including CD4 cell count, HIV viral load (VL), haemoglobin, white cell count, platelet count, urea, creatinine, albumin, lactate, C-reactive protein (CRP) and alanine transaminase (ALT), presenting diagnosis, number of organ systems affected at presentation, disposition from the ED, length of hospital stay and in-hospital mortality. The vital signs data were used to calculate the quick Sequential Organ Failure Assessment (qSOFA) score and the National Early Warning Score 2 (NEWS-2). Both qSOFA and NEWS-2 are standardised scoring tools that characterise acute illness severity, with higher scores indicating greater severity of illness and a higher risk for worse outcomes ("National Early Warning Score (NEWS) 2," 2017, "qSOFA - quick Sepsis Related Organ Failure Assessment," 2016). The various presenting diagnoses were either microbiologically or histologically confirmed or were deemed as the most likely diagnosis based on clinical assessment, special investigations and after discussion with relevant sub-speciality clinicians. Data were thereafter exported to Microsoft® Excel® (Microsoft 365, Version 16.0.13029.20232) and analysed and described using either the median and standard deviation or frequency and percentages.

Data collection commenced once ethical approval from the University of the Witwatersrand Human Research Ethics Committee (clearance certificate number: M160512) and relevant permissions were obtained. Adult patients (≥ 18 years) known to be living with HIV, including those newly diagnosed, were prospectively enrolled into the study between 07 July 2017 and 18 October 2018. As per the CMJAH ED protocol, besides patients that are already HIV-positive (either self-reported or confirmed on laboratory records of patients that previously attended the facility), all other patients attending the ED are offered HIV-rapid diagnostic testing to determine their HIV status. As per the National Department of Health (DoH) protocol, and after obtaining consent, two different HIV-rapid diagnostic tests were performed where the HIV status was

unknown. Blood was initially tested with the Abon HIV 1/2/0 Tri-line Rapid test (Abon Biopharm, Hangzhou, RR China). Reactive samples were subjected to a second confirmatory rapid test, namely, the First Response HIV 1–2.0 card (PMC Medical India Pvt, Ltd, Daman, India). Patients testing positive with both, that is, newly diagnosed as HIV-positive, were also approached for study consent and participation. For patients in whom the first test was positive, but the second test was negative, whole blood was drawn and sent to the laboratory for an enzyme-linked immunosorbent assay (ELISA) HIV-test. These were only approached for study participation if the confirmatory test was positive.

3.4 Results

During the data collection period, 29 416 patients presented to the adult medical ED triage area, of which 11 383 were triaged into the ED for further management. The remaining patients were referred to an appropriate facility in accordance with the CMJAH ED triage protocol. A total of 1308 patients were HIV-positive, of which 84 were excluded from the study as informed consent could not be obtained. A total of 1 224 participants were included in the final study sample.

Table 2 describes the median (IQR) age of study participants. The median (IQR) age of the entire cohort was 36 (IQR 31–44) years, with the median (IQR) age of men being older than that of women. Other demographic characteristics, new diagnosis with HIV, ART initiation and adherence, vital signs and laboratory findings of study participants are presented in Table 3. Most participants were women (*n* = 673, 55.0%), black (*n* = 1 174, 95.9%), single (*n* = 937, 76.6%) and had completed secondary school as the highest level of education (*n* = 1 195, 97.6%). Those who were not South African nationals comprised a fifth (*n* = 253, 20.7%) of study participants.

Table 2: Description of the median (IQR) age of study participants

Variable	Entire cohort	Male	Female
Age (years) [median (IQR)]	36 (31-44)	38 (32-45)	35 (30-43)

Approximately one-sixth of participants (*n* = 212, 17.3%) were newly diagnosed with HIV at presentation. Of the 1012 participants who were diagnosed with HIV prior to ED presentation, 761 (75.2%) were on ART. Of these, 245 (32.2%) were non-adherent as per the ACTG-AQ self-

report questionnaire. Respiratory rate was > 20 breaths/min in 434 (38.8%) participants, oxygen saturation was < 90% in 196 (17.5%), systolic blood pressure was < 90 millimetre of mercury (mmHg) in 116 (10.4%), heart rate was > 110 beats/ min in 565 (50.6%) and GCS was < 15 in 221 (19.2%) participants.

The overall median CD4 cell count and HIV VL were 112 (IQR, 34–295) cell/mm^3 and 8815 (37–325 898) copies/mL, respectively. Almost half of the study participants (*n* = 527, 47.6%) had a CD4 cell count of < 100 cell/mm^3, whilst more than half (*n* = 619, 59.0%) had a VL of > 1000 copies/mL. Amongst participants on ART who reported non-adherence, the HIV VL was > 1000 copies/mL in more than two-thirds of participants (*n* = 167, 68.2%).

Table 3: Description of demographic characteristics, HIV diagnosis, ART initiation and adherence, vital signs, and laboratory findings of study participants

Variable	**n (%)**
Demographic characteristics	
Sex	
Female	673/1224 (55.0)
Male	551/1224 (45.0)
Race	
Black	1174/1224 (95.9)
[a] Other	50/1224 (4.1)
Marital status	
Single	937/1224 (76.6)
Married	287/1224 (23.4)
Highest level of education	
Secondary school	1195/1224 (97.6)
Primary school	16/1224 (1.3)
Tertiary education	13/1224 (1.1)
Nationality	
South African	971/1224 (79.3)
Non-South African	253/1224 (20.7)
HIV diagnosis and ART initiation/ adherence	
Newly diagnosed with HIV	212/1224 (17.3)
[b] ART initiated prior to ED presentation	761/1012 (75.2)
ART non-adherence	245/761 (32.2)
Vital signs	
Respiratory rate >20 breaths/min	434/1118 (38.8)
Oxygen saturation <90%	196/1117 (17.5)
Systolic blood pressure <90 mmHg	116/1117 (10.4)
Heart rate >110 beats/min	565/1117 (50.6)
Glasgow coma scale	

15	929/1150 (80.8)
12-14	176/1150 (15.3)
9-11	38/1150 (3.3)
<9	7/1150 (0.6)
Laboratory findings	
CD4 <100 cell/mm^3	527/1105 (47.6)
HIV viral load >1000 copies/mL	619/1049 (59.0)
Haemoglobin	
>10.9 g/dL	550/1129 (48.7)
8-10.9 g/dL	366/1129 (32.4)
<8 g/dL	213/1129 (18.9)
White cell count <4.0 x 10^9/L	170/1127 (15.1)
Platelet count <150 x 10^9/L	223/1121 (19.9)
Urea >10 mmol/L	277/1069 (25.9)
Creatinine	
≤ 120 μmol/L	761/1061 (71.7)
121-200 μmol/L	129/1061 (12.2)
>200 μmol/L	171/1061 (16.1)
C-reactive protein	
≤10 mg/L	164/1059 (15.5)
11-50 mg/L	193/1059 (18.2)
51-100 mg/L	186/1059 (17.6)
>100 mg/L	516/1059 (48.7)
Lactate	
≤2.0 mmol/L	648/1118 (58.0)
2.1-5.0 mmol/L	387/1118 (34.6)
>5.0 mmol/L	83/1118 (7.4)
Albumin	
>34 g/L	408/1042 (39.1)
25-34 g/L	426/1042 (40.9)
<25 g/L	208/1042 (20.0)
Alanine transaminase >100 mmol/L	109/1029 (10.6)

The denominator has been included for all variables to account for missing data with regards to some variables.
ART – antiretroviral therapy, ED – emergency department
[a] Includes Asian, Caucasian, and mixed race
[b] Percentage calculated among participants that were known with HIV prior to ED presentation

More than half of the participants (*n* = 579, 51.3%) presented with varying degrees of anaemia (haemoglobin <11 grams per decilitre [g/dL]), whilst creatinine was >120 micromole per litre (μmol/L) in 291 (23.8%), CRP was >10 millimoles per litre (mmol/L) in 895 (74.5%), lactate was >2 mmol/L in 470 (42.0%) and albumin was <35 g/L in 634 (60.8%) participants.

Approximately one-fifth of participants (*n* = 244, 19.9%) presented with active tuberculosis (TB), of whom 70 (28.7%) had disseminated TB, whilst 143 (58.6%) had extrapulmonary TB (EPTB). The median CD4 cell count was higher, and the median HIV VL was lower amongst participants with 1) a recurrent episode of TB compared with those with a first episode, 2) TB of a single organ compared with those with disseminated TB and 3) isolated pulmonary TB (PTB) compared with those with EPTB. These and other findings pertaining to TB amongst study participants are presented in Table 4.

Table 4: Description of tuberculosis history and presentation among study participants

Variable	**n (%)**	**Median (IQR) CD4 cell count (cells/mm^3)**	**Median (IQR) HIV viral load (copies/mL)**
Previous history of tuberculosis	**294 (24.0)**	**63 (26-176)**	**97 948 (458-657 750)**
Tuberculosis at current presentation	244 (19.9)	109 (37-296)	1 740 (0-240 623)
1st episode tuberculosis	216 (88.5)	59 (25-156)	106 823 (599-659 109)
Recurrent episode tuberculosis	28 (11.5)	93 (51-252)	962 (15-422 285)
Single organ tuberculosis	174 (71.3)	82 (34-226)	25 000 (248-398 515)
Disseminated miliary tuberculosis	38 (15.6)	37 (22-87)	361 172 (7 050-1 050 000)
Disseminated non-miliary tuberculosis	32 (13.1)	42 (14-141)	157 532 (2 050-1 163 090)
[a] Pulmonary tuberculosis	101 (41.4)	89 (29-202)	130 000 (450-710 435)
Extrapulmonary tuberculosis	143 (58.6)	68 (25-154)	920 468 (288 550-2 334 203)
Miliary tuberculosis	38 (15.6)	37 (22-87)	361 172 (7 050-1 050 000)
Pleural tuberculosis	31 (12.7)	139 (56-313)	1 510 (0-69 250)
Abdominal tuberculosis	27 (11.1)	54 (25-112)	43 100 (710-475 908)
Tuberculous meningitis	23 (9.4)	104 (35-220)	141 190 (231-264 500)
Tuberculous lymphadenitis	10 (4.1)	21 (7-75)	65 200 (1 980-184 000)
Tuberculous pericarditis	9 (3.7)	65 (47-120)	3 500 (819-35 963)
Tuberculoma	4 (1.6)	150 (26-269)	48 373 (15-1 005 044)
Urogenital tuberculosis	3 (1.2)	76 (39-183)	210 064 (129 459-805 032)
Spinal tuberculosis	2 (0.8)	525 (512-537)	2 097 (1 918-2 275)
Tuberculous osteomyelitis	1 (0.4)	15 (15-15)	531 001 (531 001-531 001)

Probable cases of tuberculosis were also included as microbiological confirmation was not available for all cases

[a] Only includes participants with isolated pulmonary tuberculosis. The total number of pulmonary tuberculosis cases will be 171 (70.1%) if participants with both pulmonary and concurrent extrapulmonary tuberculosis are included.

Table 5 describes the most frequent presenting diagnoses amongst study participants and the corresponding median (IQR) CD4 cell count and HIV VL. Most participants presented with respiratory system pathology (*n* = 533, 43.5%), followed by pathology involving the

genitourinary system (*n* = 249, 20.3%), gastrointestinal system (*n* = 223, 18.2%) and central nervous system (*n* = 145, 11.8%). A total of 838 (68.4%) participants presented with an infectious disease. The most common presenting diagnoses included bacterial pneumonia (*n* = 276, 22.5%), PTB (*n* = 171, 14.0%), acute gastroenteritis (*n* = 56, 4.6%), *Pneumocystis jirovecii* pneumonia (*n* = 47, 3.8%), cryptococcal meningitis (*n* = 38, 3.1%), bacterial meningitis (*n* = 30, 2.5%) and chronic gastroenteritis (*n* = 30, 2.5%).

Table 5: The most frequent presenting diagnoses and corresponding median CD4 cell count and HIV viral load among study participants

Variable	**n (%)**	**Median (IQR) CD4 cell count (cells/mm^3)**	**Median (IQR) HIV viral load (copies/mL)**
Central nervous system	**145 (11.8)**	**106 (34-264)**	**13 480 (34-189 970)**
Cryptococcal meningitis	39 (3.2)	27 (12-72)	130 126 (1 062-300 000)
Bacterial meningitis	30 (2.5)	94 (72-170)	36 800 (12 040-224 932)
Tuberculous meningitis	23 (1.9)	104 (35-220)	141 190 (231- 264 500)
Other	53 (4.3)	272 (114-480)	37 (0-1 895)
Respiratory system	**533 (43.5)**	**71 (13-72)**	**73 300 (2 611-372 319)**
Bacterial pneumonia	276 (22.5)	77 (20-212)	75 800 (221-592 500)
Pulmonary tuberculosis	171 (14.0)	89 (29-202)	130 000 (450-710 435)
Pneumocystis jirovecii pneumonia	47 (3.8)	27 (18-90)	429 862 (98 057-551 510)
Other	39 (3.2)	275 (124-406)	144 (0-4 670)
Cardiovascular system	**47 (3.8)**	**232 (84-440)**	**680 (0-20 860)**
Congestive cardiac failure	18 (1.5)	225 (114-351)	100 (0-308 000)
Other	29 (2.3)	233 (68-419)	1 870 (10-8 855)
Gastrointestinal system	**223 (18.2)**	**97 (32-259)**	**1 850 (20-393 239)**
Acute gastroenteritis	56 (4.6)	94 (25-243)	5 500 (345-874 500
Chronic gastroenteritis	30 (2.5)	50 (11-177)	72 334 (389-496 905)
Abdominal tuberculosis	27 (3.0)	54 (25-112)	43 100 (710-475 908)
Tuberculous medication induced hepatitis	18 (1.5)	55 (45-95	20 475 (218-776 000)
Other	92 (7.5)	208 (64-400)	45 (0-118 750)
Genitourinary system	**249 (20.3)**	**94 (25-289)**	**1 550 (42-230 426)**
Acute kidney injury	138 (11.3)	57 (19-162)	3 636 (40-400 000)
Chronic kidney disease	25 (2.0)	41 (15-115)	5 500 (582-288 500)
Acute on chronic kidney disease	22 (1.8)	67 (20-220)	4 050 (43-175 989)
Urosepsis	19 (1.6)	300 (98-643)	108 (31-6 580)
Pelvic inflammatory disease	14 (1.1)	298 (196-421)	581 (0-1 295)
Other	31 (2.5)	353 (188-402)	498 (13-48 565)
Psychiatric	**78 (6.4)**	**320 (110-476)**	**37 450 (217-227 750)**
HIV associated neurocognitive disorder	15 (1.2)	138 (74-298)	305 480 (81 075-858 500)
Parasuicide intentional overdose	14 (1.1)	402 (300-424)	10 (0-3 273)

Schizophrenia	14 (1.1)	355 (98-453)	8 360 (3 790-49 668)
Substance induced psychosis	13 (1.1)	340 (162-569)	48 325 (252-244 394)
Other	24 (1.9)	397 (111-553)	20 844 (228-296 000)
Skin & soft tissue	**49 (4.0)**	**252 (72-417)**	**39 090 (6 318-933 323)**
Kaposi's sarcoma	13 (1.1)	89 (42-187)	917 518 (409 512-3 585 400)
Cellulitis	8 (0.7)	282 (243-548)	2 602 (5-28 070)
Herpes zoster	6 (0.5)	122 (18-142)	48 000 (8 465-816 000)
Other	23 (1.9)	318 (55-434)	6 050 (63-272 358)
Haematological system	**58 (4.7)**	**125 (49-244)**	**248 (22-184 000)**
Deep vein thrombosis	20 (1.6)	152 (97-247)	195 (21-88 600)
Lymphoma	11 (0.9)	79 (62-127)	86 727 (40 218-262 547)
Pulmonary embolism	10 (0.8)	379 (168-425)	155 (60-734 297)
Thrombotic thrombocytopenic purpura	5 (0.4)	48 (31-199)	75 500 (102-624 000)
Other	12 (1.0)	42 (10-152)	2 260 (220-213 000)

Just over one-third presented with pathology affecting one organ system (*n* = 460, 37.6%) or two organ systems (*n* = 432, 35.2%), whilst the remainder (*n* = 332, 27.2%) had pathology affecting three or more organ systems.

Table 5 describes the qSOFA and NEWS-2 illness severity scores, patient disposition from the ED, length of hospital stay and in-hospital mortality of study participants. Of note, 196 (17.5%) had a high qSOFA score (≥ 2 points), 496 (44.4%) had a high NEWS-2 score (≥ 7 points), 813 (66.5%) required admission to the general ward and 205 (16.7%) required intensive care unit (ICU) admission. The median length of hospital stay was 4.9 (3.5–8.0) days, with approximately one-third (*n* = 394, 32.2%) requiring admission for ≥ 7 days. The overall mortality amongst study participants was 13.6% (*n* = 166).

3.5 Discussion

To our knowledge, this is the largest single-centre study, describing the presentation of PLWH to an ED in SSA. Noteworthy findings include the large proportion of participants presenting with undiagnosed HIV, ART-treatment naivety/non-adherence, elevated HIV VL whilst on ART, other deranged laboratory parameters, HIV-related acute illness, and in-hospital mortality.

During the early days of the HIV epidemic and before the introduction of highly active antiretroviral therapy, hospital admission rates amongst PLWH were substantially higher, and

predominantly because of opportunistic infections and other acquired immunodeficiency syndrome (AIDS)-defining illnesses (Meijide et al., 2017). With the widespread introduction of effective ART, the life expectancy of PLWH is approaching that of the general population, and hospital admissions in these regions have begun to reflect age-related chronic illnesses or comorbidities rather than HIV-related acute illnesses (H. Y. Yang et al., 2019).

It is well established that the early initiation of ART and efforts to optimise ART adherence have been highly effective in curtailing the transmission of HIV and reducing HIV-associated morbidity and mortality (Albert et al., 2014; Gakhar et al., 2013; Mannheimer et al., 2002; Tapson, 2008). Hence, it is of concern that despite the free availability of ART to all South African PLWH (Cullinan, 2016), over two-thirds of study participants presented with opportunistic infections and other HIV-related acute illnesses. The high percentage of participants with CD4 cell counts < 100 cell/mm3 (47.6%), HIV VL > 1000 copies/mL (59.0%) and the large number of participants newly diagnosed with HIV (17.3%), or naïve to ART (24.9%) and those non-adherent to ART (32.2%) highlight the need for an urgent public health response and the implementation of innovative strategies to improve current HIV awareness and educational programmes, as well as to increase the rates of ART initiation, ART adherence and retention in care.

A previous systematic review and meta-analysis that included 313 006 pooled adult patients from 99 studies conducted in 50 countries, with studies being mostly conducted between 2007 and 2015 and reflecting a time when access to ART had become more widespread than before this period, reported that HIV and AIDS-related illnesses (46%) and bacterial infections (31%) were the most common reasons for hospital admission in all geographical regions. Acquired immunodeficiency syndrome-related illnesses were mostly non-bacterial opportunistic infections (Ford et al., 2015). Comparatively, in this study, a slightly lower proportion (68.4%) of participants presented with an infectious aetiology (bacterial and non-bacterial), fewer participants were diagnosed with HIV at presentation (17.3% vs. 30%), more were on ART (75.1% vs. 43%), the median length of hospital stay was shorter (4.3 days vs. 9 days) and in-hospital mortality was lower (13.6% vs. 20%). Despite this, the median CD4 cell count was lower (112 cells/mm3 vs. 168 cells/mm3) in this study. Additionally, there was a higher

percentage of participants in this study with bacterial pneumonia (22.5% vs. 15%) and TB (19.9% vs. 18%), whilst a lower percentage of patients were admitted with Pneumocystis jirovecii pneumonia (3.8% vs. 8%) and gastroenteritis (7.1% vs. 9%). Also, there were more cases of EPTB (58.6%) than isolated PTB (41.4%) in this study, in contrast to the pooled studies in which 67% presented with PTB. As the meta-analysis represented a wider demographic pool of patients, this may be a likely reason for the difference between findings of that study and this study.

A separate systematic review and meta-analysis consisting of 56 pooled studies conducted in SSA, which investigated trends in CD4 cell count at presentation to a medical facility between 2002 and 2013, found that the mean estimated CD4 cell count was 251 cells/mm^3 in 2002 and 309 cells/mm3 in 2012, with no significant annual increase over the entire period. However, of the 13 studies conducted in SA, a significant increase in the CD4 cell count of 39.9 cells per annum ($p = 0.02$) was noted from 2002 to 2013. The overall mean CD4 cell count of the 13 studies conducted in SA was 257 cell/mm^3 (Siedner et al., 2014) whereas in the current study this was lower (209 cell/mm^3). This study is unique in that it was conducted at a tertiary-level facility, which excluded patients with low acuity conditions as they were triaged to lower-level care facilities. However, the aforementioned meta-analysis included studies conducted at 'prevention of mother to child transmission (PMTCT) clinics and other lower level of care centres, which may explain the lower mean CD4 cell count observed in this study.

With regard to other findings of this study, anaemia in HIV-positive patients has been shown to be an independent predictor of clinical response, with a study showing that severe anaemia at baseline was associated with 13 times higher risk of death within the first year of ART initiation (Yesuf et al., 2019). Another study showed that increasing severity of anaemia was associated with higher rates of TB and mortality and was superior to the CD4 cell count as a predictive marker in patients on ART (Kerkhoff et al., 2015).

Acute kidney injury was reported in 11.3% of study participants. Other studies reported rates of acute renal dysfunction of 2.9% – 18% (Franceschini et al., 2005; Lopes et al., 2011; Wyatt et al., 2006), with the incidence being still high in the post-ART era.28 Similar to findings of this

study, acute renal dysfunction has been reported more commonly in patients with a low CD4 cell count and high HIV VL (Franceschini et al., 2005).

With regard to other significant study findings, the relatively high number of participants with an elevated CRP (84.5%), hypoalbuminemia (60.8%), hyperlactatemia (42%), thrombocytopaenia (19.9%) and a high qSOFA score (17.5%) is in line with the large number of participants presenting with severe illnesses. Previous studies have shown that elevated CRP (Lau, 2006), albuminemia (Sudfeld et al., 2013), hyperlactatemia (Tantisiriwat et al., 2001), thrombocytopaenia (Johannessen et al., 2008) and higher qSOFA scores (Aluisio et al., 2018; Maphula et al., 2020) were predictors of mortality and poor outcomes in HIV-positive individuals.

3.6 Limitations

Limitations of this study are that this was a single-centre study, and that data were collected over a relatively short duration of 15 months. Also, with regard to the median CD4 cell count and HIV VL values described in Tables 3 and 4, we did not account for differences between participants who were on ART and those who were not on ART or were ART non-adherent. Furthermore, as the study was conducted at a tertiary-level academic hospital and excluded patients with less severe presenting illnesses, our cumulative findings are likely to be an overestimate and not be fully reflective of the wider HIV-positive population residing within the drainage area of the hospital. A further limitation is the lack of data on chronic comorbid diseases, such as hypertension and diabetes, and the absence of follow-up outcomes post-discharge.

3.7 Conclusion

Despite the passage of more than 30 years of the HIV pandemic in Africa, PLWH are still at risk of serious morbidity and inappropriate mortality. In order to achieve the target of ending HIV by 2030 in SA, a more urgent public health response is required. This must include more innovative strategies to improve HIV awareness, new thoughts with regard to prevention, upgrading of ART services and dedication to the retention of all PLWH in care.

Acknowledgements

The authors would like to thank the staff at the Charlotte Maxeke Johannesburg Academic Hospital for their assistance with identifying potential study participants.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

A.E.L. was the primary author and was responsible for the study design, data collection, data analysis, manuscript write-up, revision, and approval of the final manuscript. W.D.F.V., G.A.R. and F.P. assisted with the study design, interpretation of results, revision of the manuscript and approval of the final manuscript.

Funding information

This research was self-funded and did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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CHAPTER 4: ARTICLE 2

The manuscript was published in the journal *South African Medical Journal* on 02 August 2021: doi:10.7196/SAMJ.2021.v111i7.15604. The journal is indexed in PubMed, Web of Science (Impact Factor 1.31) and Scopus (CiteScore 0.72).

ART non-adherence among HIV-positive patients presenting to an emergency department in Johannesburg: associations and reasons

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4.1 Abstract

Background: Suboptimal antiretroviral therapy (ART) adherence is associated with viral resistance, opportunistic infections, and increased mortality.
Objectives: To determine the rates of ART non-adherence and its associations, and also the reasons for ART non-adherence, among HIV-positive patients presenting to a major central hospital emergency department (ED).

Methods: Consecutive HIV-positive patients presenting to the Charlotte Maxeke Johannesburg Academic Hospital adult ED between 7 July 2017 and 18 October 2018 were prospectively enrolled. Self-reported adherence was assessed using the AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ).
Results: Of the 1 224 consecutive HIV-positive participants enrolled, 761 (75.2%) were on ART at the time of ED presentation. Of these, 245 (32.2%) were non-adherent as per the ACTG-AQ. Participants not yet on ART prior to ED presentation had significantly higher in-hospital mortality than participants on ART (odds ratio 1.69; 95% confidence interval 1.21 - 2.34; p=0.002). Younger age, male sex, CD4 count <100 cells/μL, lack of viral suppression, a high National Early Warning Score 2 (≥7 points) and length of hospital stay ≥7 days were significantly associated with ART non-adherence (p<0.05). Forgetfulness (13.9%) and lack of social support, depression/stress/mental illness, and lack of money for transport to collect medications (9.9% each) were the most common reasons given for ART non-adherence.
Conclusions: Of HIV-positive patients presenting to the ED, a high proportion were either not yet initiated on ART or ART non-adherent. HIV programmes should focus on HIV-positive ED attendees with the aim of identifying high-risk patients and providing adequate ART adherence support.

Keywords
HIV, emergency department, ART, adherence, non-adherence, CD4 cell count, HIV viral load

4.2 Introduction

Sub-Saharan Africa has the highest prevalence of HIV in the world, with more than two-thirds of the global cases (Shisan et al., 2014). In 2019, South Africa (SA) had an estimated 7.5 million people living with HIV (PLWH), more than any other country in the world. The most current Joint United Nations Program on HIV/AIDS (UNAIDS) data report estimates that 92% of PLWH in SA are aware of their status, 70% are on antiretroviral therapy (ART), and 64% are virally suppressed ("UNAIDS Data 2020," 2020).

The use of ART in PLWH has been associated with improvement in health-related quality of life and an overall reduction in the transmission of HIV (Albert et al., 2014; Gakhar et al., 2013),

whereas suboptimal adherence has been associated with a reduction in rates of viral suppression and an increase in rates of viral resistance, opportunistic infections, progression to AIDS and mortality (Arnsten et al., 2001; Bangsberg et al., 2001; Low et al., 2016; Mannheimer et al., 2002; Maphula et al., 2020). In 2014, UNAIDS set a target for 90% of persons diagnosed with HIV to be on sustained ART by the year 2020 ("90-90-90 An ambitious treatment target to help end the AIDS epidemic," 2014). Studies have shown that in order to achieve optimal viral suppression, ART adherence must be maintained above 90 - 95% (Bangsberg et al., 2001; Paterson et al., 2000; Turner, 2002).

ART has been made available at SA public sector healthcare facilities since 2004, with significant strides over recent years in making ART more accessible to PLWH (Abdool Karim et al., 2009). Currently there are ~5 million South Africans on ART, which is freely available at >3 500 healthcare facilities across the country (Bekker et al., 2014; "UNAIDS Data 2020," 2020). Over the past decade, criteria for the initiation of ART in SA have gradually been relaxed in line with the World Health Organization recommendations, and as of September 2016, all HIV-positive patients, irrespective of their CD4 cell count or stage of disease, are considered eligible for ART initiation (Cullinan, 2016).

ART adherence rates have been measured by various methods including patient self-reporting, pill counts, pharmacy records, electronic medication monitoring devices, and laboratory evidence of virological or immunological failure (Turner, 2002). In comparison with alternative measures of adherence, there is a tendency for patient self-reporting to overestimate ART adherence (Arnsten et al., 2001). However, owing to its ease of use, this method remains widely used (Berg and Arnsten, 2006).

There is a lack of data pertaining to the rates of ART adherence and reasons for poor adherence among HIV-positive patients presenting to the emergency department (ED) with an acute illness. Because acutely ill HIV-positive patients frequently present with opportunistic infections and related pathology, we hypothesised that the rate of suboptimal adherence would be high in this group. Findings pertaining to other aspects of this study have been published separately (Laher et al., 2021a, Laher et al., 2021b).

4.3 Methods

This was a cross-sectional study conducted at the adult medical ED at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). CMJAH is a 1 088-bed tertiary-level academic hospital affiliated to the University of the Witwatersrand. The adult medical ED manages all non-trauma patients ≥16 years of age. On arrival in the ED triage area, patients are briefly assessed and categorised as 'emergency' (red), 'very urgent' (orange), 'urgent' (yellow) or 'routine' (green), based on specific criteria as defined by the South African Triage Scale (Bruijns et al., 2008). Because CMJAH is a tertiary-level facility, patients who are categorised as red, orange, or yellow are generally managed at the facility, while stable patients who are categorised as green are referred to an alternative facility. Additionally, clinically stable patients not residing within the drainage area of the facility are referred to an alternative facility closer to the patient's home.

As per the facility protocol, apart from patients already known to be HIV-positive (either self-reported or confirmed on laboratory records of patients who had previously attended the facility), all other patients attending the ED are offered HIV rapid diagnostic testing to determine their HIV status. Whole-blood samples of patients consenting to HIV testing are tested with the Abon HIV 1/2/0 Tri-Line rapid test (Abon Biopharm, China), with reactive samples being subjected to a second confirmatory rapid test (First Response HIV 1-2.0 card, PMC Medical India Pvt Ltd, India). If the first test is positive but the confirmatory test is negative, a sample of whole blood is collected and sent to the laboratory for enzyme-linked immunosorbent assay HIV testing.

Data collection commenced once ethics clearance (University of the Witwatersrand Human Research Ethics Committee, ref. no. M160512) and relevant permissions had been obtained. Adult patients aged ≥18 years who had previously tested positive for HIV, as well as those newly diagnosed with HIV after undergoing testing in the ED, were prospectively enrolled into the study between 7 July 2017 and 18 October 2018. They included HIV-positive patients who required admission as well as patients who were directly discharged from the ED but excluded patients who were referred to another facility from the triage section. In addition, HIV-negative

patients, patients with unknown HIV status who did not consent to HIV testing, and patients who did not consent to study participation were excluded.

Prior to the commencement of data collection, informal training pertaining to the methodology and principles of data collection from medical charts was undertaken by the primary investigator. After all doctors employed in the ED had been briefed regarding the study objectives and design, they were requested to inform the primary investigator of all HIV-positive patients being managed in the ED. Written informed consent for study participation was obtained from potential participants by either the primary investigator or the doctor on shift. In the event that participants were unable to grant consent (e.g., decreased level of consciousness), consent was obtained from the next of kin/legal guardian and later from the participant if their mental capacity improved. ED registers were also reviewed daily in an effort to identify potential participants who may have been missed by the ED doctors.

The four-question AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ) was utilised to determine non-adherence to ART: (i) have you missed your antiretroviral therapy pills yesterday; (ii) have you missed your antiretroviral therapy pills the day before yesterday; (iii) have you missed your antiretroviral therapy pills during the past weekend; and (iv) have you missed your antiretroviral therapy pills in the past 2 weeks (Chesney et al., 2000). Patients who responded ‘yes’ to any of the questions were considered to be ART non-adherent and were further engaged to explore reasons for non-adherence. The questionnaire was administered to all participants who had been prescribed ART at any time in the past.

For the purposes of the study, virological failure was defined as an HIV viral load (VL) >1 000 copies/mL measured at ED presentation, and viral suppression was defined as an HIV VL <50 copies/mL measured at ED presentation.

Data were extracted from the patient’s hospital file by the primary investigator and electronically entered into an anonymised and standardised data collection form that was created in the REDCap system (Harris et al., 2009). Additional information relevant to the study but not found in the patient’s hospital records was directly obtained from the participant, the participant’s

laboratory records, or the participant's next of kin/legal guardian where applicable. Only where the next of kin/legal guardian indicated that they were aware of the participant's HIV status, were they questioned regarding relevant HIV history such as treatment adherence. Data from hospital records were collected daily over the entire duration of hospital stay or until data collection was completed. Inter-rater reliability was assessed by an independent researcher experienced in the methods of data collection and blinded to the study objectives. Data extracted from a random sample of 43 medical charts were compared with data extracted by the primary investigator.

Data relevant to this study included demographic details, HIV status, prior ART history including non-adherence, reasons for ART non-adherence, CD4 cell count and VL measured during the current presentation, hospital length of stay and in-hospital mortality. In addition, data pertaining to respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate and Glasgow Coma Scale score were collected and used to calculate the quick Sequential Organ Failure Assessment (qSOFA) score and the National Early Warning Score 2 (NEWS-2). Both the qSOFA score and the NEWS-2 are standardised scoring tools that characterise acute illness severity, with higher scores indicating greater severity of illness and a higher risk of worse outcomes ("National Early Warning Score (NEWS) 2," 2017, "qSOFA - quick Sepsis Related Organ Failure Assessment," 2016).

Data were exported to Microsoft Excel (Office 365, 16.0.13029.20232; Microsoft, USA) and thereafter to Stata version 16 (StataCorp, USA) for statistical analysis. Frequencies and percentages were determined for categorical variables. Depending on the frequency of participants in each group, either Pearson's $\chi 2$ test or Fisher's exact test was used to determine whether there were significant differences between the two groups. Since data for continuous variables were not normally distributed, medians and interquartile ranges (IQRs) were calculated, while the Mann-Whitney rank-sum test was used to determine whether there were significant differences between the two groups. The two groups were further analysed by univariate logistic regression, and odds ratios (ORs) for ART non-adherence were determined for each of the variables. A two-sided p-value <0.05 was considered significant throughout. Study reporting conformed with the STROBE (Strengthening the Reporting of Observational Studies

in Epidemiology) guidelines (Elm et al., 2007).

4.4 Results

During the data collection period, 29 416 patients presented to the adult medical ED triage area, of whom 11 383 were triaged into the ED for further management. The remaining patients were referred to an appropriate facility in accordance with the CMJAH ED triage protocol. A total of 1 308 patients were HIV-positive, of whom 84 were excluded from the study because informed consent could not be obtained.

A total of 1 224 HIV-positive participants were included in the final study sample. Approximately one-sixth of the participants were newly diagnosed with HIV (n=212; 17.3%). Participants who were newly diagnosed had a significantly lower median (IQR) CD4 cell count (81 (22.5 - 171.5) cells/μL v. 125 (35.5 - 332) cells/μL; $p<0.001$) and a significantly higher median (IQR) HIV VL (253 500 (36 150 - 913 193.5) copies/mL v. 1 400 (10 - 215 502.5) copies/mL; $p<0.001$) than participants who had been diagnosed prior to ED presentation.

Of the 1 012 participants (82.7%) who had been diagnosed with HIV prior to ED presentation, 761 (75.2%) were on ART, of whom 516 (67.8%) were adherent and 245 (32.2%) non-adherent as per the ACTG-AQ self-report questionnaire utilised in the study. The median age of participants on ART was 37 (interquartile range 31 - 44) years, with the majority being female (n=460; 60.4%), unmarried (n=587; 77.1%) and having completed secondary school as the highest level of education (n=748; 98.3%).

Table 6 describes and compares demographic characteristics, including the number of participants with a CD4 cell count <100 cells/μL the number presenting with virological failure, the number presenting with viral suppression, the median qSOFA score, the median NEWS-2, the median length of hospital stay and in-hospital mortality, between participants who were ART adherent and those who were non-adherent.

Table 6: Characteristics of study participants

	Participants on ART	ART adherent	ART non-adherent	OR (95% CI)	P-value
Age (years) [median (IQR)]	37 (31-44)	38 (32-46)	37 (29.5-43)	0.97 (0.93-0.99)	**0.001**
Sex [n (%)]					**0.011**
Female	460 (60.5)	328 (63.6)	132 (53.9)	1.00 (Reference)	
Male	301 (39.5)	188 (36.4)	113 (46.1)	1.49 (1.09-2.03)	
Race [n (%)]					0.693
Black	727 (95.5)	494 (95.7)	233 (95.1)	1.00 (Reference)	
[a] Other	34 (4.5)	22 (4.3)	12 (4.9)	1.16 (0.68-2.98)	
Marital status [n (%)]					0.709
Single	587 (77.1)	396 (76.7)	191 (78.0)	1.00 (Reference)	
Married	174 (22.9)	120 (23.3)	54 (22.0)	0.93 (0.65-1.34)	
Highest level of education [n (%)]					0.952
Tertiary education	5 (0.7)	4 (0.8)	1 (0.4)	1.00 (Reference)	
Primary school	8 (1.0)	6 (1.2)	2 (0.8)	1.33 (0.09-20.11)	
Secondary school	748 (98.3)	506 (98.1)	242 (98.8)	1.91 (0.21-17.21)	
Nationality [n (%)]					0.472
South Africa	623 (81.9)	426 (82.6)	197 (80.4)	1.00 (Reference)	
Non-South African	138 (18.1)	90 (17.4)	48 (19.6)	1.15 (0.78-1.70)	
CD4 cell count <100 cell/mm^3 [n (%)]	275 (40.9)	141 (29.7)	134 (68.0)	5.03 (3.52-7.21)	**<0.001**
[b] Virological failure [n (%)]	235 (37.1)	68 (15.5)	167 (86.5)	35.13 (21.58-57.21)	**<0.001**
[c] Viral suppression [n (%)]	251 (39.7)	241 (54.8)	10 (5.2)	0.02 (0.01-0.04)	**<0.001**
qSOFA score [n (%)]					
Low score (0-1 point)	562 (82.4)	416 (83.9)	146 (78.5)	1.00 (Reference)	
High score (2-3 points)	120 (17.6)	80 (16.1)	40 (21.5)	1.42 (0.93-2.18)	0.102
NEWS-2 score [n (%)]					
Low score (0-4 points)	298 (43.8)	230 (46.5)	68 (36.6)	1.00 (Reference)	
[d] Medium score (5-6 points)	109 (16.0)	78 (15.8)	31 (16.7)	1.34 (0.82-1.21)	0.243
High score (≥7 points)	274 (40.2)	187 (37.7)	87 (46.8)	1.57 (1.09-2.28)	**0.017**
Length of hospital stay ≥7 days [n (%)]	245 (32.2)	154 (29.8)	91 (37.1)	1.39 (1.01-1.91)	**0.045**
In-hospital mortality [n (%)]	85 (11.2)	50 (9.7)	35 (14.3)	1.55 (0.98-2.46)	0.062

To calculate the prevalence of CD4 <100 cell/mm^3, virological failure and virological suppression, the denominator used was the number of participants in whom CD4 cell count and HIV VL was measured. CD4 cell count and HIV VL were respectively measured in 672 (88.3%) and 633 (83.2%) participants on ART, 475 (92.1%) and 440 (85.3%) participants reporting ART adherence and, 197 (80.4%) and 193 (78.8%) participants reporting ART non-adherence.

[a] Includes Asian, Caucasian, and mixed race

[b] Virological failure defined as HIV VL >1000 copies/mL

[c] Viral suppression defined as HIV VL <50 copies/mL

[d] Includes patients with an overall low score but achieving 3 points in any individual parameter

qSOFA: quick Sequential Organ Failure Assessment

NEWS-2: National Early Warning Score 2

There were significant differences between participants who were ART adherent and those who were non-adherent with regard to age, sex, CD4 cell count <100 cells/μL, virological failure, viral suppression, NEWS-2, and length of hospital stay. Every year's increase in age was

associated with a 3% (p=0.001) lower likelihood of ART non-adherence, while males had a 49% (p=0.011) higher likelihood of ART non-adherence. Overall, those who had not been initiated on ART prior to ED presentation (n=81; 17.5%) had higher in-hospital mortality than those who had been initiated on ART (n=85; 11.2%), with the former having a 69% higher likelihood of death (OR 1.69; 95% confidence interval 1.21 - 2.34; p=0.002).

Participants with a CD4 cell count <100 cells/μL and those with virological failure had a 5.03 times (p<0.001) and 35.13 times (p<0.001) higher likelihood of ART non-adherence, respectively, whereas participants who were virally suppressed had a 98% (p<0.001) lower likelihood of ART non-adherence.

Compared with participants with a low qSOFA score (0 - 1 point) at presentation, there were no statistically significant differences with regard to ART non-adherence among those with a high qSOFA score (2 - 3 points) (p=0.102). Compared with participants with a low NEWS-2 (0 - 4 points) at presentation, those with a medium NEWS-2 (5 - 6 points overall, or an overall low score but achieving 3 points for any individual parameter) did not have a statistically significant difference with regard to ART non-adherence, but those with a high NEWS-2 (≥7 points) had a 57% (p=0.017) higher likelihood of ART non-adherence.

Participants who required hospital admission for ≥7 days had a 39% (p=0.045) higher likelihood of ART non-adherence. Although in-hospital mortality was associated with a 55% (p=0.062) higher likelihood of ART non-adherence, it did not reach (though marginally) statistical significance.

Figure 6 describes the reasons for ART non-adherence. Two hundred and twenty-nine participants (93.5%) reported a single reason for non-adherence, while the remaining 16 (6.5%) reported two reasons each. Of note, ‘Forgot to take my medication’ was reported as the most common reason (n=34; 13.9%), followed by ‘No social support’, ‘Depression/stress/mental illness’ and ‘No transport money to local clinic’ at 9.9% (n=24) each.

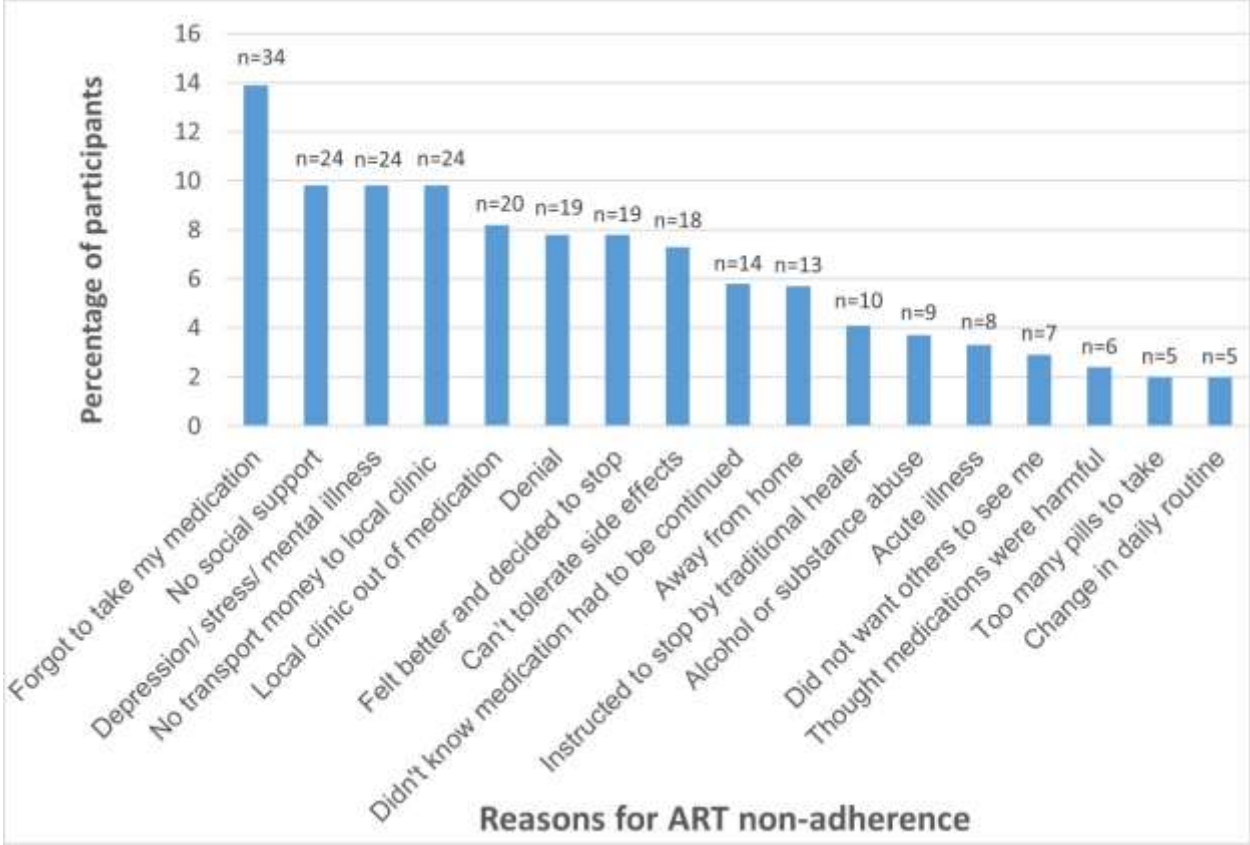


Figure 6: Reasons for ART non-adherence among study participants
Totals add up to >100% as some participants reported more than one reason

4.5 Discussion

To our knowledge, no previous studies have reported on ART adherence among acutely ill HIV-positive patients presenting to an ED in southern Africa. Most published studies relating to ART adherence were conducted in non-acutely ill patients attending outpatient ART clinics (Lal et al., 2010). Overall, our findings indicate that the ED setting is an ideal opportunity to identify high-risk HIV-positive patients.

Despite rigorous nationwide HIV awareness campaigns ("HIV/AIDS in South Africa," n.d.), approximately one-sixth of the study participants (17.2%) were only diagnosed at ED presentation. However, this figure is better than the findings by Hansoti et al. (Hansoti et al., 2018) at the Frere Hospital ED in East London, SA, where 115 out of 400 HIV-positive participants (28.75%) were newly diagnosed with HIV at ED presentation. Of concern, newly diagnosed HIV-positive participants had very low CD4 cell counts and high VLs. This finding

calls for an urgent public health response and ascertaining the reasons for this group presenting with late-stage disease should be considered a research priority. Additionally, this finding indicates the need to further improve local HIV awareness programmes with particular emphasis on the importance of early testing.

Despite ART being freely available to all PLWH in SA (Cullinan, 2016), only 83.3% of study participants diagnosed with HIV >1 month prior to ED presentation had been initiated on ART. This is, however, higher than current national figures indicating that ~70% of PLWH in SA have been initiated on ART. It may also be a reflection of the ART programme being well established in central Johannesburg. ("UNAIDS Data 2020," 2020) Furthermore, study participants who were on ART prior to ED presentation had significantly lower in-hospital mortality than those who were not on ART (p=0.002). Reduction in the rates of clinical deterioration as well as several other benefits associated with the early initiation of ART have been well described in previous studies (Cohen et al., 2011; Lee and Deeks, 2016).

As per the ACTG-AQ questionnaire used in this study, approximately a third (32.2%) of study participants on ART were non-adherent, whereas if we had relied on the presence of virological failure as a marker of non-adherence, a slightly higher percentage of participants (37.2%) would have been regarded as non-adherent. In contrast, a study conducted in 2019 in Durban, SA, among non-acutely ill patients reported ART adherence in >95% of the 270 participants who were enrolled. However, the authors used pharmacy pill counts as a measure to determine non-adherence (Moosa et al., 2019). Results of a meta-analysis that included 33 199 pooled patients from 84 studies reported an overall global rate of ART adherence of 62%. Adherence was assessed using one method only in 63 studies (75%), two methods in 20 studies (23.8%) and three methods in one study (1.2%). Self-reporting was the most frequently used technique, employed in 77 of the included studies. None of these included studies were conducted in the ED or in patients presenting with acute illness (Ortego et al., 2011).

In the present study, age and sex were significantly associated with ART adherence, with the odds of ART non-adherence being significantly higher among younger participants and males. Similarly, in a systematic review that included 146 studies conducted in sub- Saharan Africa, age

was reported in 20 of the included articles as a determinant of adherence, with poor adherence being more prominent in younger individuals overall. Among studies that reported on sex differences, 11 reported better adherence among females, while 6 reported better adherence among males (Heestermans et al., 2016).

It is not surprising that virological failure was significantly more prevalent among ART non-adherent study participants (84.5% v. 15.5%) and that viral suppression was significantly more prevalent among ART-adherent participants (54.8% v. 5.2%). Comparatively, in a study by Arnsten et al. (Arnsten et al., 2001), 62% of participants were virally suppressed. However, these authors defined viral suppression as a VL <500 copies/mL, whereas in our study we used a much lower threshold of <50 copies/mL (as per the 2019 National Department of Health guidelines ("2019 ART Clinical Guidelines for the Management of HIV in Adults, Pregnancy, Adolescents, Children, Infants and Neonates," 2019). If we had also used a higher threshold of <500 copies/mL, 77.7% of participants with reported ART adherence would have achieved viral suppression.

The facts that virological failure was still present in ~15% of ART-adherent study participants and that viral suppression was not achieved in almost half of ART-adherent participants are of concern. While pharmacokinetic drug-drug interactions and ART drug resistance may be responsible for the lack of viral suppression in some cases, ART non-adherence is more likely to be the underlying reason in most cases (Moneti et al., 2012). It is therefore possible that ART nonadherence was under-reported by study participants, and the ACTGAQ questionnaire used in this study may not have been sufficiently sensitive to identify all cases of non-adherence. A transient increase in the VL (viral 'blip'), which is common in the setting of intercurrent illness, may also have contributed to the relatively low rates of viral suppression among ART-adherent study participants (Jones and Perelson, 2005).

Similarly, a CD4 count <100 cells/µL was identified in almost one-third of ART-adherent study participants (29.7%). Taking into consideration that a low CD4 cell count may be a prominent feature in any patient with acute illness (independent of the underlying HIV status) (Feeney et al., 1995), this finding may well account for the relatively high number of participants with a low

CD4 cell count. In the setting of acute intercurrent illness, the presence of a low CD4 cell count and a high HIV VL may therefore not necessarily be reliable indicators of ART treatment failure.

Furthermore, the significantly higher proportion of ART non-adherent participants presenting with a high NEWS-2 and also requiring a longer hospital length of stay (≥7 days), and the trend towards higher in-hospital mortality in ART non-adherent participants, indicate that this group presented with more severe illness.

In the present study, 'forgetfulness' (13.9%), followed by 'lack of social support', 'depression/stress/mental illness' and 'no transport money to collect medication' (n=24, 9.9% each) were reported as the most frequent reasons for ART non-adherence. In a study that also used the ACTG-AQ to determine non-adherence among 200 patients attending an ART clinic in New Delhi, India, ART nonadherence was reported in 10% of participants, with 'travel' (10.5%) and 'forgetfulness' (9.5%) reported as the most frequent reasons (Lal et al., 2010). A separate study that used a modified ACTG questionnaire to assess non-adherence among 151 patients in Mississippi, USA, reported that 47.7% of patients were non-adherent.[37] In contrast to our study, the authors reported the most frequent reasons as 'not having the medication with them' (39%), 'sleeping through the dose time' (25%), 'running out of the medication' (22%), and 'being busy with other things' (21%) (Amico et al., 2007).

In a recent study conducted in Uganda, 20% of participants reported ART side-effects or fear of side-effects as the reason for non-adherence, while 26.7% indicated that alternative medicines were preferred over ART (Bukenya et al., 2019). Comparatively, in the present study, 7.3% of respondents reported intolerable side-effects as the reason, while 4.1% reported that they were instructed to stop their ART by a traditional healer.

A systematic review and meta-analysis that included 125 studies across 38 countries with ~19 016 pooled participants cited the most frequently reported reasons for ART non-adherence among adult patients as forgetfulness (41.4%), being away from home (30.4%), a change in daily routine (28.0%), depression (15.5%), alcohol/substance misuse (12.9%), secrecy/stigma (13.6%), feeling sick (15.9%) and pharmacy stock-outs (16.1%) (Shubber et al., 2016). In comparison, in

the present study, frequency rates for the above reasons were as follows: forgetting (13.9%), being away from home (5.7%), a change in daily routine (2.0%), depression (9.8%), alcohol/substance misuse (3.7%), secrecy/stigma (2.9%), feeling sick (3.3%) and pharmacy stock-outs (8.2%).

4.6 Limitations

There are some limitations to this study. Firstly, measurement of adherence was reliant on the ACTG-AQ questionnaire, which only determined ART adherence over the 2 weeks before ED presentation. This may have resulted in under-reporting of overall adherence, as some participants may have been non-adherent prior to the 2 weeks before ED presentation but were more adherent in the past 2 weeks owing to the onset of symptoms of acute illness. Fear of being reprimanded, the acuity of the presenting illness and reliance on information from the next of kin or relatives may be other reasons for inaccurate reporting of ART adherence. Although reasons for a low CD4 cell count and virological failure were not explored, it is likely that the relatively high proportion of ART-adherent participants with a high VL and low CD4 cell count may also indicate that ART nonadherence rates were possibly higher than reported.

4.7 Conclusion

HIV-positive participants not initiated on ART and presenting with acute illness to the ED had significantly higher mortality than HIV-positive participants who had been initiated on ART. Younger age, male sex, CD4 count <100 cells/μL, virological failure, lack of viral suppression, a higher NEWS-2, and length of hospital stay >5 days were significantly associated with ART non-adherence among acutely ill HIV-positive patients presenting to the ED. There is a need for improved local HIV awareness and educational programmes, and for these programmes to further emphasise the importance of early testing, early initiation of ART and ART adherence.

Acknowledgements

The authors would like to thank the staff at the Charlotte Maxeke Johannesburg Academic Hospital for their assistance with identifying potential study participants.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

A.E.L. was the primary author and was responsible for the study design, data collection, data analysis, manuscript write-up, revision, and approval of the final manuscript. W.D.F.V., G.A.R. and F.P. assisted with the study design, interpretation of results, revision of the manuscript and approval of the final manuscript.

Funding information

This research was self-funded and did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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CHAPTER 5: ARTICLE 3

The manuscript was published in the journal *PLoS One* on 21 April 2021: doi:10.1371/journal.pone.0249706. The journal is indexed in PubMed, Web of Science (Impact Factor 2.74) and Scopus (CiteScore 5.2).

Predictors of prolonged hospital stay in HIV-positive patients presenting to the emergency department

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5.1 Abstract

Background: Prolonged hospitalization places a significant burden on healthcare resources. Compared to the general population, hospital length of stay (LOS) is generally longer among HIV-positive patients.
Objectives: To identify predictors of prolonged hospital length of stay (LOS) among HIV-positive patients presenting to an emergency department (ED).

Methods: In this cross-sectional study, HIV-positive patients presenting to the Charlotte Maxeke Johannesburg Academic Hospital adult ED were prospectively enrolled between 07 July 2017 and 18 October 2018. Data was subjected to univariate and multivariate logistic regression to determine parameters associated with a higher likelihood of prolonged hospital LOS, defined as ≥7 days.

Results: Among the 1 224 participants that were enrolled, the median (IQR) LOS was 4.6 (2.6–8.2) days, while the mean (SD) LOS was 6.9 (8.2) days. On multivariate analysis of the data, haemoglobin <11 g/dL (OR 1.37, p = 0.032), Glasgow coma scale (GCS) <15 (OR 1.80, p = 0.001), creatinine >120 μmol/L (OR 1.85, p = 0.000), cryptococcal meningitis (OR 2.45, p = 0.015) and bacterial meningitis (OR 4.83, p = 0.002) were significantly associated with a higher likelihood of LOS ≥7 days, while bacterial pneumonia (OR 0.35, p = 0.000) and acute gastroenteritis (OR 0.40, p = 0.025) were significantly associated with a lower likelihood of LOS ≥7 days.

Conclusion: Various clinical and laboratory parameters are useful in predicting prolonged hospitalization among HIV-positive patients presenting to the ED. These parameters may be useful in guiding clinical decision making and directing the allocation of resources.

Keywords

HIV; emergency department; prolonged hospitalization, hospital length of stay; LOS

5.2 Introduction

South Africa has an estimated 7.5 million people living with HIV (PLWH), which equates to approximately one-fifth of the global burden of the disease ("UNAIDS Data 2020," 2020). With the widespread availability of antiretroviral therapy (ART) over recent years, there has been a significant reduction in HIV-related hospitalization rates, hospital length of stay (LOS) and mortality (Coelho et al., 2017; Jones et al., 2019). Despite this, HIV still ranked as the 3rd highest cause of global mortality in 2019 ("Top 10 leading causes of death in the world from 1990-2019 complete ranking," 2019, "UNAIDS Data 2020," 2020) Furthermore, HIV contributes significantly to healthcare costs (Ritchwood et al., 2017).

Compared to those attending HIV clinics, HIV-positive patients presenting to the emergency

department (ED) tend to be more severely ill and frequently require hospitalization and admission to the intensive care unit (ICU) (Barbour et al., 2009; Maphula et al., 2020). The average hospital LOS among HIV-positive patients requiring admission varies widely from approximately 4 days to over 15 days (Álvarez Barreneche et al., 2017; Barbour et al., 2009; Dias et al., 2009; Krentz et al., 2006). Compared to HIV-negative patients, those with HIV have higher rates of hospitalization and a longer LOS (Krentz et al., 2006). Besides being associated with poorer clinical outcomes, prolonged LOS also places a significant burden on healthcare resources. In fact, a large proportion of the overall financial burden relating to HIV has been attributed to the cost of in-hospital care and treatment of acutely ill HIV-positive patients(Barbour et al., 2009; Jones et al., 2019).

There is a paucity of published data pertaining to factors that predict the length of hospitalization in HIV-positive patients presenting to the ED (Gonçalves and Ferreira, 2013; Santella et al., 2010). In addition to guiding clinical
management, the identification of these factors may assist clinicians with triage and the appropriate channelling of resources, particularly in resource limited environments. Therefore, the aim of this study was to determine predictors of prolonged hospital stay (LOS ≥7 days) in HIV-positive patients presenting to the ED. Findings pertaining to other aspects of this study have been published separately (Laher et al., 2021a; Laher et al., 2021b, Laher et al., 2021c).

5.3 Methods

This was a cross-sectional study that was conducted at the adult medical-ED unit of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). CMJAH is a 1088 bed tertiary-level academic hospital affiliated to the University of the Witwatersrand. The adult medical ED unit manages all non-trauma patients that are ≥16 years of age. On arrival to the ED triage area, patients are briefly assessed and categorized as either “emergent” (red), “very urgent” (orange), “urgent” (yellow) or “routine” (green), based on specific criteria as defined by the South African Triage Scale (Bruijns et al., 2008). Since CMJAH is a tertiary level facility, in general patients that are categorized as red, orange, or yellow are managed at the facility, while stable patients that are categorized as green are referred to an alternate facility. Additionally, clinically stable

patients not residing within the drainage area of the facility are also referred to an alternate facility closer to the patient's residence.

As per the facility protocol, besides patients that are already HIV-positive (either self-reported or confirmed on laboratory records of patients that previously attended the facility), all other patients attending the ED are offered HIV-rapid diagnostic testing to determine their HIV status. Whole blood samples of patients consenting to HIV testing are tested with the Abon HIV 1/2/0 Tri-line Rapid test (Abon Biopharm, Hangzhou, RR China), with reactive samples thereafter subjected to a second confirmatory rapid test (First Response HIV 1–2.0 card, PMC Medical India Pvt, Ltd, Daman, India). In those in whom the first test is positive, but the confirmatory test is negative, a sample of whole blood is collected and sent to the laboratory for ELISA HIV-testing.

Data collection commenced once ethics clearance (University of the Witwatersrand Human Research Ethics Committee- clearance certificate number M160512) and relevant permissions were obtained. The ethics application included participant consent procedures that were also reviewed and approved by the committee. Adult patients ≥18 years that previously tested positive for HIV as well as those newly diagnosed with HIV after undergoing testing in the ED were prospectively enrolled into the study between 07 July 2017 and 18 October 2018. This included HIV-positive patients that required admission as well as patients that were directly discharged from the ED but excluded patients that were referred to another facility from the triage section. In addition, HIV-negative patients, HIV-status unknown patients who did not consent to HIV testing and patients not consenting to study participation were excluded.

Prior to the commencement of data collection, informal training pertaining to the methodology and principles of data collection from medical charts was undertaken by the primary investigator. After briefing all doctors employed in the ED regarding the study aim, objectives, and design they were requested to inform the primary investigator of all HIV-positive patients being managed in the ED. Written informed consent for study participation was obtained from potential participants by either the primary investigator or the doctor on shift. In the event that participants were unable to grant consent (e.g., decreased level of consciousness), consent was

obtained from the next of kin/legal guardian and later re-obtained from the participant in the event that their mental capacity had improved. ED registers were also reviewed daily in an effort to identify potential participants that may have been missed by the ED doctors. For the purpose of this study, prolonged hospitalization was defined as LOS ≥7 days.

The four question AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ) was utilized to determine non-adherence to ART (Chesney et al., 2000). Patients that responded "yes" to any of the questions were regarded as being ART non-adherent. The questionnaire was administered to all participants who had been prescribed ART at any time in the past.

Data was extracted from the patient's hospital file by the primary investigator and electronically entered into an anonymized and standardized data collection form that was created in the RedCap system (Harris et al., 2009). Additional information relevant to the study but not found in the patient's hospital records was directly obtained from the participant, the participants laboratory records, or the participants next of kin/ legal guardian where applicable. Only where the next of kin/ legal guardian indicated that they were aware of the participant's HIV status, they were questioned regarding relevant HIV-history such as treatment adherence. Data from hospital records were collected daily over the entire duration of hospital stay or until data collection was completed. Inter-rater reliability was assessed by an independent researcher experienced in the methods of data collection and blinded to the study aims and objectives. Data extracted from a random sample of 43 medical charts were compared to data extracted by the primary investigator.

Data relevant to this study included demographic details, HIV status, prior ART history including non-adherence, vital signs at presentation, results of relevant laboratory tests that were performed during the current presentation, presenting diagnoses, number of organ systems affected at presentation, disposition from the ED, length of hospital stay and in-hospital mortality. The vital signs data were also used to calculate the quick Sequential Organ Failure Assessment (qSOFA) score and the National Early Warning Score 2 (NEWS-2). The qSOFA score combines three rapid bedside clinical criteria (GCS <15, respiratory rate ≥22 breaths per minute and systolic blood pressure ≤100 mmHg) and is aimed at identifying patients that are at

higher risk of in-hospital mortality ("qSOFA - quick Sepsis Related Organ Failure Assessment," 2016). The NEWS-2 score combines six criteria (respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate and level of consciousness) and is aimed at determining severity of illness and prompting critical care interventions in patients being monitored in hospital ("National Early Warning Score (NEWS) 2," 2017). The various presenting diagnoses were either microbiologically or histologically confirmed or were deemed as the most likely diagnosis based on findings of clinical assessment and special investigations and after discussion with the relevant sub-specialty clinician.

Data was exported to Microsoft® Excel® (Microsoft 365, Version 16.0.13029.20232) and thereafter to Stata version 16 (StataCorp Limited, Texas, United States of America) for statistical analysis. Besides age, all other continuous variables were categorized based on cut-offs frequently reported in the literature (e.g., CD4 cell count <100 cell/mm^3; albumin <35 g/L etc.). Linearity was assessed using scatterplots. Frequency and percentage were determined for categorical variables. Depending on the number of participants in each group, either the Pearson's chi-square or the Fisher's exact test was used to determine if there were significant differences between the two groups.

The data was further subjected to univariate as well as multivariate analysis to determine factors influencing in-hospital mortality while accounting for possible confounders such as age. On univariate analysis, binary logistic regression was used to determine factors associated with LOS ≥7 days. Crude odds ratio (OR) was reported with 95% confidence interval (CI) and p-value. For each of the variables assessed in the univariate analysis, all available case information was utilized. In the multivariate model, patients with missing data for the included variables were dropped from the model. All variables with a p-value of <0.1 in the univariate analysis were evaluated in the multivariate analysis. Non-significant variables were dropped with stepwise backward regression. To assess for interactions, interaction terms were individually added between variables in the multivariate model. Co-linearity was assessed via the Variance Inflation Factor (VIF) with values of >10 regarded as indicative of multicollinearity. A two-sided p-value of <0.05 was considered significant throughout. Study reporting was in conformance with

STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Elm et al., 2007).

5.4 Results

A total of 11 383 of 29 416 patients that presented to the triage area of the adult medical ED over the period of data collection were managed in the ED, with the remainder being referred to an alternate appropriate facility as per the departmental triage protocol. Among those that were managed in the ED, 1308 were HIV-positive, however, 84 did not consent to study participation. Hence, the final study sample comprised 1224 patients (Laher et al., 2021a; Laher et al., 2021b, Laher et al., 2021c). The median (IQR) and mean (SD) LOS was 4.6 (2.6-8.2) days and 6.9 (8.2) days, respectively. The LOS was ≥7 days in 394 (32.2%) participants.

Comparisons and OR for LOS ≥7 days with respect to demographic details, HIV diagnosis, ART initiation/ adherence, vital signs and laboratory parameters are described in table 7. There were no statistically significant differences between participants with LOS ≥7 days and those <7 days ($p < 0.05$) with regard to demographic characteristics and data pertaining to HIV diagnosis and ART initiation/ adherence. With regard to vital signs at presentation, the likelihood of LOS ≥7 days was lower (OR 0.66, $p = 0.021$) among those presenting with an oxygen saturation <90%, while it was more than two times higher (OR 2.36, $p < 0.001$) among those with a GCS <15. There were no statistically significant differences with regards to the other vital signs parameters that were analysed. With regards to laboratory findings, the likelihood of LOS ≥7 days was higher among those presenting with a lactate >2.0 mmol/L (OR 1.32, $p = 0.029$), an albumin <35 g/L (OR 1.33, $p = 0.039$), a haemoglobin <11 g/dL (OR 1.50, $p = 0.002$), a urea >10 mmol/L (OR 1.97, $p < 0.001$) and a creatinine >120 μmol/L (OR 1.98, $p < 0.001$). There were no statistically significant differences with regards to any other laboratory parameters that were analysed.

Table 7: Comparison of LOS with respect to demographic details, HIV diagnosis, ART initiation/ adherence, vital signs, and laboratory parameters of study participants

	Entire cohort	Length of admission		OR (95% CI)	P-value
		<7 days	≥7 days		
Demographic characteristics					
Age (years) [median (IQR)]	36 (31-44)	36 (30-43)	37 (31-44)	0.99 (0.98-1.01)	0.279
Sex [n (%)]					0.868
Female	673 (55.0)	447 (53.9)	226 (57.4)	1.00 (Reference)	
Male	551 (45.0)	383 (46.1)	168 (42.6)	0.87 (0.68-1.10)	
Race [n (%)]					0.119
Black	1174 (95.9)	791 (95.3)	383 (97.2)	1.00 (Reference)	
[a] Other	50 (4.1)	39 (4.7)	11 (2.8)	0.58 (0.30-1.15)	
HIV diagnosis and ART initiation/ adherence					
Newly diagnosed HIV [n (%)]	212 (17.3)	150 (18.1)	62 (15.7)	0.84 (0.61-1.17)	0.313
ART initiated prior to ED presentation [n (%)]	761 (62.2)	508 (61.2)	253 (64.2)	1.13 (0.89-1.46)	0.311
ART non-adherent [n (%)]	245 (32.2)	154 (30.3)	91 (23.1)	1.32 (0.98-1.77)	0.064
Vital signs					
Respiratory rate >20 breaths/min [n (%)]	434 (38.8)	303 (39.1)	131(38.1)	0.95 (0.74-1.24)	0.736
Oxygen saturation <90% [n (%)]	196 (17.5)	149 (19.3)	47 (13.6)	0.66 (0.46-0.94)	**0.021**
Systolic blood pressure <90 mmHg [n (%)]	116 (10.4)	81 (10.5)	35 (10.2)	0.97 (0.64-1.47)	0.878
Heart rate >110 beats/min [n (%)]	565 (50.6)	379 (49.1)	186 (53.9)	1.21 (0.94-1.56)	0.137
Glasgow coma scale <15 [n (%)]	221 (19.2)	117 (14.8)	104 (29.1)	2.36 (1.75-3.19)	**<0.001**
Laboratory findings					
CD4 <100 cell/mm^3 [n (%)]	527 (47.6)	344 (46.0)	183 (51.1)	1.23 (0.95-1.58)	0.110
HIV viral load >1000 copies/mL [n (%)]	619 (59.0)	428 (59.4)	191 (58.2)	0.95 (0.73-1.24)	0.730
Haemoglobin <11 g/dL [n (%)]	579 (51.3)	374 (48.1)	205 (58.2)	1.50 (1.17-1.94)	**0.002**
White cell count <4.0 x 10^9/L [n (%)]	170 (15.1)	117 (15.1)	53 (15.1)	1.01 (0.71-1.43)	0.971
Platelet count <150 x 10^9/L [n (%)]	223 (19.9)	155 (20.1)	68 (19.5)	0.97 (0.70-1.33)	0.843
Urea >10 mmol/L [n (%)]	277 (25.9)	159 (21.7)	118 (35.2)	1.97 (1.48-2.61)	**<0.001**
Creatinine >120 µmol/L [n (%)]	300 (24.5)	173 (23.8)	127 (38.1)	1.98 (1.50-2.62)	**<0.001**
C-reactive protein >100 mg/L [n (%)]	516 (48.7)	339 (47.0)	177 (52.5)	1.25 (0.96-1.62)	0.092
Lactate >2 mmol/L [n (%)]	470 (42.0)	307 (39.9)	163 (46.8)	1.32 (1.03-1.71)	**0.029**
Albumin <35 g/L [n (%)]	633 (60.7)	418 (58.6)	215 (65.3)	1.33 (1.01-1.75)	**0.039**
Alanine transaminase >100 mmol/L [n (%)]	109 (10.6)	70 (10.0)	39 (11.9)	1.22 (0.80-1.84)	0.356

OR – Odds ratio, ART – antiretroviral therapy, ED – emergency department
Bold – denotes statistical significance
[a] Includes Asian, Caucasian, and mixed race

Comparisons and OR for LOS ≥7 days with respect to common HIV-related presenting diagnoses, illness severity scores, ICU admission and in-hospital mortality are described in table 8. With regards to the presenting diagnoses, the likelihood of LOS ≥7 days was higher in those that presented with tuberculosis (OR 1.66, p ,0.001), with participants that were diagnosed with abdominal tuberculosis (OR 2.31, p =0.031) and tuberculous meningitis (OR 4.07, p =0.002) showing the highest likelihood of LOA ≥7 days. Among those with cryptococcal and bacterial

meningitis, the likelihood for LOS ≥7 days was approximately two and a half times (OR 2.54, p =0.004) and just over six times (OR 6.08, p <0.001) higher, respectively. The likelihood for LOS ≥7 days was lower among those with bacterial pneumonia (OR 0.37, p <0.001).

Compared to participants presenting with pathology affecting a single organ system, there was no significant difference in LOS ≥7 days among those presenting with pathology affecting two organ systems (p =0.863), but however, those with pathology affecting ≥3 organ systems had almost a one and half times higher likelihood of LOS ≥7 days (OR 1.49, p =0.008).

The qSOFA and NEWS-2 scores were not significantly associated with LOS ≥7 days (p >0.05 for both), however, the likelihood of LOS ≥7 days was higher among those that required ICU admission (OR 1.75, p <0.001) as well as among those that died during hospital admission (OR 1.56, p =0.010).

After adjusting for oxygen saturation and removing participants with missing data, variables with a p-value <0.1 from the univariate analysis were subjected to multivariate logistic regression. A total of 1027 (83.9%) participants were included in the final model (table 9). Haemoglobin <11 g/dL (OR 1.37, p =0.032), GCS <15 (OR 1.80, p =0.001), creatinine >120 μmol/L (OR 1.85, p =0.000), cryptococcal meningitis (OR 2.45, p =0.015) and bacterial meningitis (OR 4.83, p =0.002) were significantly associated with a higher likelihood of LOS ≥7 days, while bacterial pneumonia (OR 0.35, p =0.000) and acute gastroenteritis (OR 0.40, p =0.025), were significantly associated with a lower likelihood of LOS ≥7 days.

Table 8: Comparison of LOS with respect to common HIV related presenting diagnoses, illness severity scores, ICU admission and in-hospital mortality of study participants

	Entire cohort (n, %)	**Length of admission**		**OR (95% CI)**	**P-value**
		<7 days (n, %)	**≥7 days (n, %)**		
Tuberculosis	**244 (19.9)**	**143 (17.2)**	**101 (25.6)**	**1.66 (1.24-2.21)**	**<0.001**
Single organ tuberculosis	174 (14.2)	103 (12.4)	71 (18.0)	1.62 (1.16-2.25)	**0.005**
Disseminated tuberculosis	70 (5.7)	40 (4.8)	30 (7.6)	1.63 (1.00-2.66)	**0.049**
[a] Pulmonary tuberculosis	101 (8.3)	65 (7.8)	36 (9.1)	1.18 (0.77-1.81)	0.438
Extrapulmonary tuberculosis	143 (11.7)	78 (9.4)	65 (16.5)	1.90 (1.34-2.71)	**<0.001**
Miliary tuberculosis	38 (3.1)	21 (2.5)	17 (4.3)	1.74 (0.91-3.33)	0.096
Pleural tuberculosis	31 (2.5)	23 (2.8)	8 (2.0)	0.73 (0.32-1.64)	0.443

Abdominal tuberculosis	27 (2.2)	13 (1.6)	14 (3.6)	2.31 (1.08-4.97)	**0.031**
Tuberculous meningitis	23 (1.9)	8 (1.0)	15 (3.8)	4.07 (1.71-9.67)	**0.002**
[b] Other	29 (2.4)	16 (1.9)	13 (3.3)	1.74 (0.83-3.65)	0.145
Bacterial pneumonia	276 (22.5)	228 (27.5)	48 (12.2)	0.37 (0.26-0.51)	**<0.001**
Pneumocystis jirovecii pneumonia	47 (3.8)	37 (4.4)	10 (2.5)	0.56 (.027-1.13)	0.11
Cryptococcal meningitis	39 (3.2)	18 (2.2)	21 (5.3)	2.54 (1.34-4.82)	**0.004**
Bacterial meningitis	30 (2.5)	8 (1.0)	22 (5.6)	6.08 (2.68-13.78)	**<0.001**
Acute gastroenteritis	56 (4.6)	44 (5.3)	12 (3.0)	0.56 (0.29-1.07)	0.08
Chronic gastroenteritis	30 (2.5)	19 (2.2)	11 (2.8)	1.23 (0.58-2.60)	0.60
No. of organ systems affected					
1	460 (37.6)	324 (39.0)	136 (34.5)	1.00 (Reference)	
2	432 (35.2)	302 (36.4)	130 (33.0)	1.03 (0.77-1.37)	0.863
≥3	332 (27.2)	204 (24.6)	128 (32.5)	1.49 (1.11-1.01	**0.008**
qSOFA score					
Low score (0-1 point)	921 (82.5)	642 (82.9)	279 (81.3)	1.00 (Reference)	
High score (2-3 points)	196 (17.5)	132 (17.2)	64 (18.7)	1.12 (0.80-1.55)	0.516
NEWS-2 score					
Low score (0-4 points)	449 (40.2)	316 (40.9)	133 (38.7)	1.00 (Reference)	
[c] Medium score (5-6 points)	171 (15.4)	111 (14.4)	60 (17.4)	1.28 (0.88-1.87)	0.189
High score (≥7 points)	496 (44.4)	345 (44.7)	151 (43.9)	1.04(0.79-1.37)	0.783
ICU admission	205 (16.7)	117 (14.1)	88 (22.3)	1.75 (1.29-2.38)	**<0.001**
In-hospital mortality	166 (13.6)	98 (11.8)	68 (17.2)	1.56 (1.11-2.18)	**0.010**

OR – Odds ratio

Bold – denotes statistical significance

[a] Only includes participants with isolated pulmonary tuberculosis

[b] Tuberculous lymphadenitis (n=10), tuberculous pericarditis (n=9), tuberculoma (n=4), urogenital tuberculosis (n=3), spinal tuberculosis (n=2), tuberculous osteomyelitis (n=1)

[c] Includes participants with an overall low score but achieving 3 points in any individual parameter

Table 9: Variables significantly associated with LOS ≥7 days after subjecting the relevant data to multivariate analysis

Parameter	Multivariate analysis	
	OR (95% CI)	P-value
Haemoglobin <11 g/dL	1.37 (1.03-1.83)	**0.032**
Glasgow coma scale <15	1.80 (1.28-2.54)	**0.001**
Creatinine >120 μmol/L	1.85 (1.36-2.52)	**0.000**
Cryptococcal meningitis	2.45 (1.19-5.05)	**0.015**
Bacterial meningitis	4.83 (1.82-12.82)	**0.002**
Bacterial pneumonia	0.35 (0.23-0.52)	**0.000**
Acute gastroenteritis	0.40 (0.18-0.89)	**0.025**

OR – Odds ratio

Model adjusted for oxygen saturation

5.5 Discussion

To our knowledge, this is the largest and most comprehensive single-centre study to have determined predictors of prolonged hospital admission in consecutive HIV-positive patients admitted via the ED. In fact, overall, there are very few studies that have reported parameters that predict prolonged hospital stay among HIV-positive patients and these studies have examined a very limited number of parameters. As such comparison of the findings of this study to others is difficult.

In 2 studies conducted in Rhode Island, USA (Barbour et al., 2009) and Calgary, Canada (Krentz et al., 2006) the median LOS was 4.7 and 5 days respectively among hospitalized HIV-positive patients, which was comparable with the median LOS in this study at 4.6 days. In contrast, in a longitudinal study of hospitalized HIV-positive patients conducted in Rio de Janeiro, Brazil, the authors reported a much longer median LOS of 15 days in 2007 and 11 days in 2013, with a longer median LOS in patients admitted with AIDS related illnesses than those admitted for non-AIDS related illnesses (Coelho et al., 2017). Although we did not directly compare patients with and without AIDS defining illnesses, subsets of patients with tuberculosis, cryptococcal meningitis and bacterial meningitis had a significantly higher likelihood of a prolonged LOS. Studies conducted in Portugal and Columbia among hospitalized HIV-positive patients also reported a longer median LOS of 12 (Dias et al., 2009) and 14 days (Álvarez Barreneche et al., 2017) respectively.

With regard to the specific factors associated with a longer LOS, a longitudinal study conducted in Portugal between 2009-2014 found that the number of secondary diagnoses, the number of inpatient procedures, and tuberculosis were associated with a longer LOS, whereas female gender, emergent admission, in-hospital mortality, pneumocystis jirovecii pneumonia and hepatitis C were all associated with a shorter LOS (Augusto et al., 2019). Furthermore, the study conducted in Calgary, Canada reported that a low CD4 cell count, presence of an AIDS defining illness and no current use of ART were strongly correlated with hospitalization ($p < 0.01$) (Krentz et al., 2006). Additionally, a study that retrospectively evaluated the effect of various factors on hospital LOS in Louisiana, USA between 1998 and 2003, reported that gender and age were non-significant predictors, while the number of comorbid conditions and inpatient procedures and the

presence of an AIDS defining diagnosis were significant independent predictors (Santella et al., 2010). Another study conducted in Brazil, reported that low income was associated with prolonged LOS among HIV-positive patients with tuberculosis (Gonçalves and Ferreira, 2013). In comparison to the findings of some of the above studies, tuberculosis, multiple organ involvement (≥3 organ systems) and in-hospital mortality were associated with a longer LOS on univariate analysis, while there were no significant differences with regards to age, gender, low CD4 cell count (<100 cell/mm^3), use of ART and pneumocystis jirovecii pneumonia.

Although there is a lack of comparable data pertaining to HIV-positive patients and LOS, low GCS (Okazaki et al., 2020), anaemia (Burr et al., 1993; Nathavitharana et al., 2012; Sanoufa et al., 2015), elevated urea (Faisst et al., 2010; Toptas et al., 2018), elevated creatinine (Eghbalzadeh et al., 2018; Toptas et al., 2018), hypalbuminaemia (Burr et al., 1993; Chua et al., 2019), hyperlactatemia (Andersen et al., 2015), cryptococcal meningitis (Wu et al., 2020) and bacterial meningitis (Yerramilli et al., 2017) have been associated with prolonged LOS in multiple non-HIV based studies that enrolled general medical, perioperative and other disease-specific population groups.

It is rather surprising that those with oxygen saturation <90% had a significantly lower likelihood of prolonged LOS (OR 0.37, p <0.001). Although the underlying reason for this finding is unclear and were not explored in this study, the large number of study participants that presented with bacterial pneumonia and other respiratory system pathologies (most of whom had a LOS <7 days), may be a possible explanation. Furthermore, it is also possible that some patients with a low oxygen saturation at presentation may have demised during the initial days of their hospital admission.

5.6 Limitations

There are some limitations to this study. Firstly, this was a single centre study, hence our findings may not necessarily be generalizable to other settings where criteria for patient discharge may differ. Secondly, it is possible that some patients may have been readmitted for the same illness shortly after having been discharged, which was not taken into account when calculating the LOS. Thirdly, some patients were discharged for continuation of care to a

rehabilitation or step-down facility, which was also not accounted for when calculating the LOS. Finally, we did not account for the presence of underlying comorbid and other chronic illnesses, nor did we account for individual social circumstances, both of which may have also influenced the overall LOS.

5.7 Conclusion

There are specific criteria that predict longer length of stay in HIV-positive patients presenting to the ED. These findings may be useful in guiding clinical decision making, directing the appropriate channelling of resources, and facilitating the design of innovative strategies to optimize LOS.

Acknowledgements

The authors would like to thank the staff at the Charlotte Maxeke Johannesburg Academic Hospital for their assistance with identifying potential study participants.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

A.E.L. was the primary author and was responsible for the study design, data collection, data analysis, manuscript write-up, revision, and approval of the final manuscript. W.D.F.V., G.A.R. and F.P. assisted with the study design, interpretation of results, revision of the manuscript and approval of the final manuscript.

Funding information

This research was self-funded and did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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CHAPTER 6: ARTICLE 4

The manuscript was published in the journal *HIV Medicine* on 31 August 2021: doi:10.1111/hiv.13097. The journal is indexed in PubMed, Web of Science (Impact Factor 3.55) and Scopus (CiteScore 5.8).

Predictors of in-hospital mortality among HIV-positive patients presenting with an acute illness to the emergency department

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6.1 Abstract

Background: Despite better access to antiretroviral therapy (ART) over recent years, HIV remains a major global cause of mortality.

Objectives: The present study aimed to identify predictors of in-hospital mortality among HIV-positive patients presenting to an emergency department (ED).
Methods: In this cross-sectional study, HIV-positive patients presenting to the Charlotte Maxeke Johannesburg Academic Hospital adult ED between 07 July 2017 and 18 October 2018 were prospectively enrolled. Data were compared between participants who survived to hospital discharge and those who died. The data were further subjected to univariate and multivariate logistic regression analyses to determine variables that were associated with in-hospital mortality.
Results: Of a total of 1 224 participants, the in-hospital mortality was 13.6% (n = 166). On multivariate analysis, respiratory rate > 20 breaths/min [odds ratio (OR) = 1.90, P = 0.012], creatinine > 120 mmol/L (OR = 1.97, P = 0.006), oxygen saturation < 90% (OR = 2.09, P = 0.011), white cell count < 4.0 9 109/L (OR = 2.09, P = 0.008), ART non-adherence or not yet on ART (OR = 2.39, P = 0.012), Glasgow Coma Scale < 15 (OR = 2.53, P = 0.000), albumin < 35 g/L (OR = 2.61, P = 0.002), lactate > 2 mmol/L (OR = 4.83, P = 0.000) and cryptococcal meningitis (OR = 6.78, P = 0.000) were significantly associated with in-hospital mortality.
Conclusions: Routine clinical and laboratory parameters are useful predictors of in-hospital mortality in HIV-positive patients presenting to the ED with an acute illness. These parameters may be of value in guiding clinical decision-making, directing the appropriate use of resources, and influencing patient disposition, and may also be useful in developing an outcome prediction tool.

Keywords
acute illness, antiretroviral therapy, CD4 cell count, emergency department, HIV, HIV survival, HIV viral load, in-hospital mortality, opportunistic infections

6.2 Introduction

Globally, there are approximately 38 million people living with HIV (PLWH) ("UNAIDS Data 2020," 2020). From 2003 to 2009, HIV was the leading cause of death worldwide, with the annual mortality peaking at just under 1.4 million deaths in 2007 ("Top 10 leading causes of death in the world from 1990-2019 complete ranking," 2019). Better availability and improved access to antiretroviral therapy (ART) over the past 15 years has resulted in a significant

reduction in HIV mortality (690 000 deaths in 2019), such that HIV now ranks as the third highest cause of global deaths after cardiovascular disease and cancer ("Top 10 leading causes of death in the world from 1990-2019 complete ranking," 2019, "UNAIDS Data 2020," 2020).

South Africa has approximately one-fifth of the world's HIV cases, with an overall HIV prevalence of 20.4% ("Global information and education on HIV and AIDS - HIV and AIDS in South Africa," 2020). In 2017, HIV was reported to be the fifth highest cause of mortality in South Africa ("Stats SA statistical release P0309.3 - Mortality and causes of death in South Africa: Findings from death notification 2017," 2020). South Africa currently boasts the world's largest HIV programme, the success of which is evident from an increase in life expectancy of 56 years in 2010 to 63 years in 2018 ("World Bank - Data country profile: South Africa," 2019). Although there has been a 47% reduction in new HIV infections and a 40% reduction in HIV-related deaths from 2010 to 2019, the burden of HIV is still substantial, with c.200 000 new HIV infections and 72 000 HIV-related deaths reported in South Africa in 2019 ("UNAIDS Data 2020," 2020). The high mortality associated with HIV has had far-reaching socioeconomic consequences, including a reduction in labour supply, agricultural productivity, human capital and national development as well as an upsurge in widow-and-orphan-headed households (Parker et al., 2009; Russell et al., 2007).

Previous studies conducted in both outpatient and inpatient non-emergency department (ED) settings have indicated that various clinical and laboratory parameters such as the presenting diagnosis, requiring admission to the intensive care unit (ICU), a low CD4 cell count, an elevated HIV viral load (VL), anaemia, renal dysfunction, albuminemia, hyperlactataemia etc. have been associated with a higher likelihood of mortality in HIV-positive patients (Franceschini et al., 2005; Kerkhoff et al., 2015; Maphula et al., 2020; Siedner et al., 2014; Sudfeld et al., 2013; Tantisiriwat et al., 2001). However, there is a lack of data emanating from the ED setting. In addition to guiding timely management such as the early initiation of empirical antimicrobial therapy, judicious haemodynamic resuscitation, fast-tracking of special investigations and early ICU admission, the prompt identification of factors associated with poor outcomes at ED presentation may also assist clinicians with the appropriate channelling of resources, particularly in environments where these are limited. Hence, the aim of this study was to determine variables

that may be associated with a higher likelihood of in-hospital mortality in HIV-positive patients presenting to the ED with an acute illness. Identifying such variables may also potentially be useful for developing a predictive tool to identify HIV-positive patients with higher risk of mortality.

6.3 Methods

This was a cross-sectional study that was conducted at the adult medical ED unit of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The CMJAH is a 1088-bed tertiary-level academic hospital affiliated to the University of the Witwatersrand. The adult medical ED unit manages all non-trauma patients who are ≥ 16 years of age. On arrival to the ED triage area, patients are briefly assessed and categorized as 'emergent' (red), 'very urgent' (orange), 'urgent' (yellow) or 'routine' (green), based on specific criteria as defined by the South African Triage Scale (Bruijns et al., 2008). As the CMJAH is a tertiary-level facility, in general patients who are categorized as red, orange, or yellow are managed at the facility, while stable patients who are categorized as green are referred to an alternate facility. Additionally, clinically stable patients not residing within the drainage area of the facility are also referred to an alternate facility closer to the patient's residence.

As per the facility protocol, besides patients who are already HIV-positive (either self-reported or confirmed on laboratory records of patients who previously attended the facility), all other patients attending the ED are offered HIV-rapid diagnostic testing to determine their HIV status. Whole-blood samples of patients consenting to HIV testing are tested with the Abon HIV 1/2/0 Tri-line Rapid test (Abon Biopharm, Hangzhou, China), with reactive samples thereafter subjected to a second confirmatory rapid test (First Response HIV 1–2.0 card' PMC Medical India Pvt Ltd, Daman, India). In those in whom the first test is positive, but the confirmatory test is negative, a sample of whole blood is collected and sent to the laboratory for enzyme-linked immunosorbent assay (ELISA) HIV testing.

Data collection commenced once ethics clearance (University of the Witwatersrand Human Research Ethics Committee, clearance certificate number M160512) and relevant permissions were obtained. Adult patients ≥ 18 years who previously tested positive for HIV as well as those

newly diagnosed with HIV after undergoing testing in the ED were prospectively enrolled into the study between 7 July 2017 and 18 October 2018. This included HIV-positive patients who required admission as well as patients who were directly discharged from the ED but excluded patients who were referred to another facility from the triage section. In addition, HIV-negative patients, HIV-status-unknown patients who did not consent to HIV testing and patients not consenting to study participation were excluded.

Prior to the commencement of data collection, informal training pertaining to the methodology and principles of data collection from medical charts was undertaken by the primary investigator. After briefing all doctors employed in the ED regarding the study aim, objectives, and design, they were requested to inform the primary investigator of all HIV-positive patients being managed in the ED. Written informed consent for study participation was obtained from potential participants by either the primary investigator or the doctor on shift. In the event that participants were unable to grant consent (e.g., decreased level of consciousness), it was obtained from the next of kin/legal guardian and later re-obtained from the participant in the event that their mental capacity had improved. Emergency department registers were also reviewed daily in an effort to identify potential participants who may have been missed by the ED doctors.

The four-question AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ) was utilized to determine non-adherence to ART (Chesney et al., 2000). Patients who responded ‘yes’ to any of the questions were regarded as being ART nonadherent. The questionnaire was administered to all participants who had been prescribed ART at any time in the past.

Data were extracted from the patient’s hospital file by the primary investigator and electronically entered into an anonymized and standardized data collection form that was created in the RedCap system (Harris et al., 2009). Additional information relevant to the study but not found in the patient’s hospital records was obtained directly from the participant, the participant’s laboratory records, or the participant’s next of kin/legal guardian, where applicable. Only where the next of kin/legal guardian indicated that they were aware of the participant’s HIV status, were they questioned regarding relevant HIV history such as treatment adherence. Data from hospital records were collected daily over the entire duration of hospital stay or until data

collection was completed. Interrater reliability was assessed by an independent researcher experienced in the methods of data collection and blinded to the study aims and objectives. Data extracted from a random sample of 43 medical charts were compared with data extracted by the primary investigator.

Data relevant to this study included demographic details, HIV status, prior ART history including non-adherence, vital signs at presentation, results of relevant laboratory tests that were performed during the current presentation, presenting diagnoses, number of organ systems affected at presentation, disposition from the ED, length of hospital stay and in-hospital mortality. The vital signs data were also used to calculate the quick Sequential Organ Failure Assessment (qSOFA) score and the National Early Warning Score 2 (NEWS-2). The qSOFA score combines three rapid bedside clinical criteria [Glasgow Coma Scale (GCS) < 15, respiratory rate ≥ 22 breaths/min and systolic blood pressure ≤ 100 mmHg) and is aimed at identifying patients who are at higher risk of in-hospital mortality ("qSOFA - quick Sepsis Related Organ Failure Assessment," 2016). The NEWS-2 score combines six criteria (respiratory rate, oxygen saturation, temperature, systolic blood pressure, heart rate and level of consciousness) and is aimed at determining severity of illness and prompting critical care interventions in patients being monitored in hospital ("National Early Warning Score (NEWS) 2," 2017). The various presenting diagnoses were either microbiologically or histologically confirmed or were deemed to be the most likely diagnosis based on findings of clinical assessment and special investigations and after discussion with the relevant sub-specialty clinician.

Data were exported to Microsoft Excel (Microsoft 365, v.16.0.13029.20232) and thereafter to Stata v.16 (Stata- Corp Ltd, College Station, TX, USA) for statistical analysis. Besides age, all other continuous variables were categorized based on cut-offs frequently reported in the literature (e.g., CD4 cell count < 100 cells/mm^3, albumin < 35 g/L etc.). Linearity was assessed using scatterplots. Frequency and percentage were determined for categorical variables. Depending on the number of participants in each group, either the Pearson v2 or Fisher's exact test was used to determine if there were significant differences between the two groups.

The data were further subjected to univariate as well as multivariate analysis to determine factors influencing in-hospital mortality while accounting for possible confounders such as age. On univariate analysis, binary logistic regression was used to determine factors associated with in-hospital mortality. Crude odds ratio (OR) was reported with 95% confidence interval (CI) and P-value. For each of the variables assessed in the univariate analysis, all available case information was utilized. In the multivariate model, patients with missing data for the included variables were dropped from the model. All variables with a P-value < 0.1 in the univariate analysis were evaluated in the multivariate analysis. Non-significant variables were dropped with stepwise backward regression. To assess for interactions, interaction terms were individually added between variables in the multivariate model. Collinearity was assessed via the variance inflation factor with values > 10 regarded as indicative of multicollinearity. A two-sided $P < 0.05$ was considered significant throughout. Study reporting was in conformance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Elm et al., 2007).

6.4 Results

During the data collection period, 29 416 patients presented to the adult medical ED triage area, of whom 11 383 were triaged into the ED for further management. The remainder were referred to an alternate facility in accordance with the CMJAH ED triage protocol. Of the 1308 patients who were HIV-positive, 84 were excluded as informed consent could not be obtained. A total of 1224 patients were included in the final study sample. Details of how the final study sample was achieved is described in Figure 7.

A total of 166 (13.6%) participants died prior to hospital discharge. Comparisons and OR of in-hospital mortality with regard to demographic details, HIV diagnosis, ART initiation/adherence, vital signs and laboratory parameters are described in Table 10. Although the majority of participants were female (n = 673, 55.0%), the likelihood of in-hospital mortality was 49% higher in males (OR = 1.49, P = 0.017). With regard to the other demographic data collected, there were no statistically significant differences between participants who survived and those who died ($P < 0.05$). Participants who were newly diagnosed with HIV at ED presentation (OR = 1.98, $P < 0.001$) and participants who were ART non-adherent (OR = 1.64, P = 0.045) demonstrated a higher likelihood of in-hospital mortality, while participants who had been

initiated on ART before presenting to the ED (OR = 1.41, P = 0.002) demonstrated a lower risk of in-hospital mortality. All vital signs listed in Table 10 were associated with a higher likelihood of in-hospital mortality with GCS < 15 (OR = 3.66, P < 0.001) and respiratory rate > 20 breaths/min (OR = 2.17, P < 0.001) displaying the highest likelihoods. All laboratory parameters listed in Table 1 were also associated with a higher likelihood of in-hospital mortality. Notably, the likelihood of in-hospital mortality was more than three times higher among those presenting with a platelet count < 150 x 10^9/L (OR = 3.04, P < 0.001), albumin in the range 25–34 g/dL (OR = 3.06, P < 0.001), HIV viral load > 1000 copies/mL (OR = 3.16, P < 0.001), C-reactive protein (CRP) > 100 mg/L (OR = 3.30, P < 0.001), urea > 10 mmol/L (OR = 3.41, P < 0.001) and creatinine > 200 mmol/L (OR = 3.47, P < 0.001). The likelihood of in-hospital mortality was more than four times higher among participants presenting with an elevated lactate in the range 2.1–5.0 mmol/L (OR = 4.26, P < 0.001) and albumin < 25 g/L (OR = 7.52, P < 0.001), while in-hospital mortality was the highest among those with lactate > 5 mmol/L (OR = 13.19, P < 0.001).

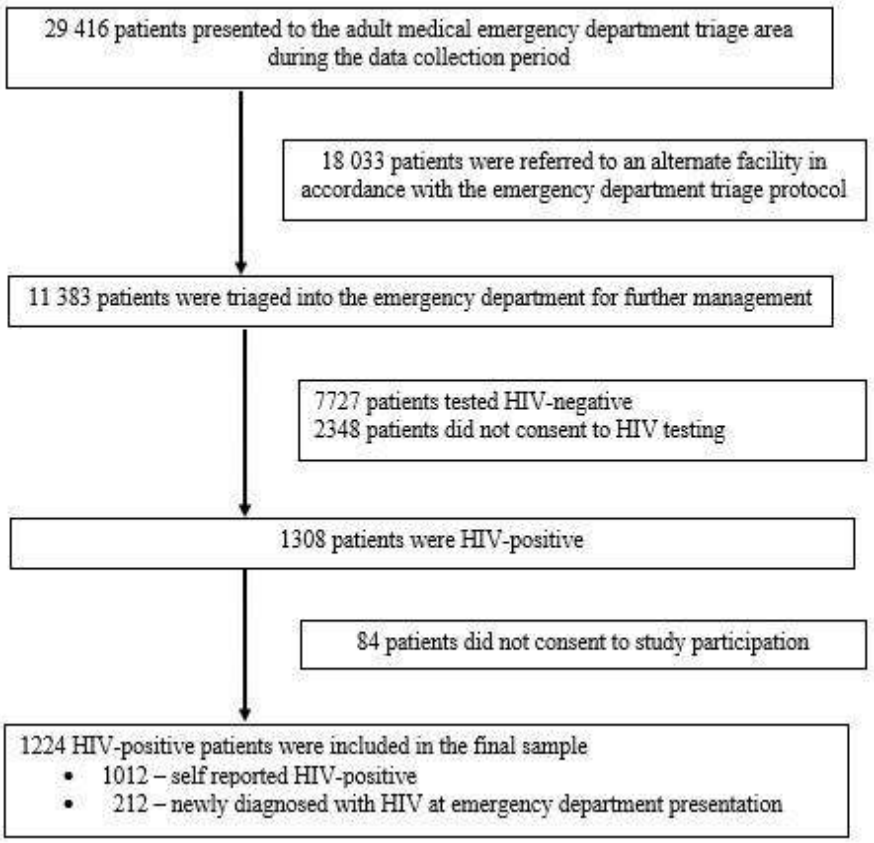


Figure 7: Description of how the final study sample was achieved

Table 10: Comparison of in-hospital mortality with regards to demographic details, HIV diagnosis, ART initiation/ adherence, vital signs, and laboratory parameters of study participants

	Entire cohort	Survival to discharge	In-hospital mortality	OR (95% CI)	P-value
Demographic characteristics					
Age (years) [median (IQR)]	36 (31-44)	36 (31-44)	38 (30-45)	1.01 (0.99-1.02)	0.328
Sex [n (%)]					**0.017**
Female	673 (55.0)	596 (56.3)	77 (46.7)	1.00 (Reference)	
Male	551 (45.0)	462 (43.7)	89 (53.6)	1.49 (1.07-2.07)	
Race [n (%)]					0.349
Black	1174 (95.9)	1017 (95.9)	157 (94.6)	1.00 (Reference)	
[a] Other	50 (4.1)	41 (3.9)	9 (5.4)	1.42 (0.68-2.98)	
Marital status [n (%)]					0.112
Single	937 (76.6)	818 (77.3)	119 (71.7)	1.00 (Reference)	
Married	287 (23.4)	240 (22.7)	47 (28.3)	1.35 (0.93-1.94)	
Highest level of education [n (%)]					0.828
Secondary school	1195 (97.6)	1034 (97.7)	161 (97.0)	1.00 (Reference)	
Primary school	16 (1.3)	13 (1.2)	3 (1.8)	1.48 (0.41-5.26)	
Tertiary education	13 (1.1)	11 (1.1)	2 (1.2)	1.17 (0.26-5.32)	
Nationality [n (%)]					0.274
South Africa	971 (79.3)	834 (78.8)	137 (82.5)	1.00 (Reference)	
Non-South African	253 (20.7)	224 (21.2)	29 (17.5)	0.79 (0.51-1.21)	
HIV diagnosis and ART initiation/ adherence					
Newly diagnosed HIV [n (%)]	212 (17.3)	167 (15.8)	45 (27.1)	1.98 (1.36-2.90)	**<0.001**
ART initiated prior to ED presentation [n (%)]	761 (62.2)	676 (63.9)	85 (51.2)	0.59 (0.43-0.82)	**0.002**
ART non-adherent [n (%)]	245 (32.2)	209 (30.9)	36 (42.3)	1.64 (1.04-2.60)	**0.045**
Vital signs					
Respiratory rate >20 breaths/min [n (%)]	434 (38.8)	349 (36.2)	85 (55.2)	2.17 (1.54-3.06)	**<0.001**
Oxygen saturation <90% [n (%)]	196 (17.5)	157 (16.3)	39 (25.3)	1.74 (1.16-2.6)	**0.007**
Systolic blood pressure <90 mmHg [n (%)]	116 (10.4)	91 (9.4)	25 (16.2)	1.86 (1.15-3.00)	**0.011**
Heart rate >110 beats/min [n (%)]	565 (50.6)	473 (49.1)	92 (59.7))	1.54 (1.09-2.17)	**0.015**
Glasgow coma scale <15 [n (%)]	221 (19.2)	157 (18.8)	64 (68.8)	3.66 (2.55-5.26)	**<0.001**
Laboratory findings					
CD4 <100 cell/mm^3 [n (%)]	527 (47.6)	433 (44.8)	94 (67.6)	2.58 (1.77-3.76)	**<0.001**
HIV viral load >1000 copies/mL [n (%)]	619 (59.0)	537 (58.1)	82 (65.6)	3.16 (2.15-4.65)	**<0.001**
Haemoglobin [n (%)]					
>10.9 g/dL	550 (48.7)	491 (50.3)	59 (38.3)	1.00 (Reference)	
8-10.9 g/dL	366 (32.4)	306 (31.4)	60 (39.0)	1.63 (1.11-2.40)	**0.013**
<8 g/dL	213 (18.9)	178 (18.3)	35 (22.7)	1.63 (1.04-2.57)	**0.033**
White cell count <4.0 x 10^9/L [n (%)]	170 (15.1)	137 (14.1)	33 (21.6)	1.68 (1.10-2.57)	**0.017**
Platelet count <150 x 10^9/L [n (%)]	223 (19.9)	165 (17.0)	58 (38.4)	3.04 (2.11-4.40)	**<0.001**
Urea >10 mmol/L [n (%)]	277 (25.9)	205 (22.2)	72 (49.3)	3.41 (2.38-4.88)	**<0.001**
Creatinine [n (%)]					
<120 µmol/L	761 (71.7)	688 (75.2)	73 (50.0)	1.00 (Reference)	
120-200 µmol/L	129 (12.2)	102 (11.1)	27 (18.5)	2.49 (1.53-4.06)	**<0.001**
>200 µmol/L	171 (16.1)	125 (13.7)	46 (31.5)	3.47 (2.29-5.25)	**<0.001**
C-reactive protein [n (%)]					

≤10 mg/L	164 (15.5)	153 (16.7)	11 (7.6)	1.00 (Reference)	
11-50 mg/L	193 (18.2)	179 (19.6)	14 (9.7)	1.09 (0.48-2.47)	0.840
51-100 mg/L	186 (17.6)	165 (18.1)	21 (14.5)	1.17 (0.83-3.79)	0.142
>100 mg/L	516 (48.7)	417 (45.6)	99 (68.3)	3.30 (1.72-6.32)	**<0.001**
Lactate [n (%)]					
<2.1 mmol/L	648 (58.0)	609 (63.6)	39 (24.4)	1.00 (Reference)	
2.1-5.0 mmol/L	387 (34.6)	304(31.7)	83 (51.9)	4.26 (2.84-6.39)	**<0.001**
>5.0 mmol/L	83 (7.4)	45 (4.7)	38 (23.8)	13.19 (7.69-22.62)	**<0.001**
Albumin [n (%)]					
>34 g/L	408 (39.1)	388 (42.8)	20 (14.8)	1.00 (Reference)	
25-34 g/L	426 (40.9)	368 (40.6)	58 (42.6)	3.06 (1.80-5.18)	**<0.001**
<25 g/L	208 (20.0)	150 (16.6)	58 (42.6)	7.52 (4.37-12.93)	**<0.001**
Alanine transaminase >100 mmol/L [n (%)]	109 (10.6)	80 (9.0)	29 (20.9)	2.67 (1.67-4.27)	**<0.001**

OR – Odds ratio, ART – antiretroviral therapy, ED – emergency department
Bold – denotes statistical significance
[a] Includes Asian, Caucasian, and mixed race

Comparisons and OR of in-hospital mortality with regard to common HIV-related presenting diagnoses, illness severity scores, disposition from the ED and length of hospital admission of study participants are described in Table 11. It is notable that those with meningitis that included tuberculous (OR = 2.87, P = 0.022), cryptococcal (OR = 2.27, P = 0.029) and bacterial (OR = 4.50, P = 0.001) subtypes all displayed significantly higher odds of in-hospital mortality. Additionally, participants presenting with pathology affecting more than one organ system displayed an incrementally higher odds of in-hospital mortality. A similar trend was noted with the qSOFA score and the NEWS-2 score. A total of 16.8% (n = 206) of participants were discharged home from the ED. Compared with participants who were admitted to the ward, those who were admitted to the ICU had an approximately three-fold (OR = 3.27, P < 0.001) higher likelihood of in-hospital mortality, and compared with participants with a length of hospital stay < 7 days, those with a hospital stay ≥ 7 days had a 56% (OR = 1.56, P = 0.010) higher likelihood of in-hospital mortality.

Table 11: Comparison of in-hospital mortality with regards to common HIV-related presenting diagnoses, illness severity scores, disposition from the ED and length of hospital admission of study participants

	Entire cohort (n, %)	Survival to discharge (n, %)	In-hospital mortality (n, %)	OR (95% CI)	P-value
Tuberculosis	244 (19.9)	203 (19.2)	41 (24.7)	1.38 (0.94-2.03)	0.099
Single organ tuberculosis	174 (14.2)	149 (14.1)	25 (15.1)	1.08 (0.68-1.71)	0.738
Disseminated tuberculosis	70 (5.7)	54 (5.1)	16 (9.6)	1.98 (1.11-3.56)	**0.021**
[a] Pulmonary tuberculosis	101 (8.3)	84 (7.9)	17 (10.2)	1.32 (0.76-2.29)	0.999
Extrapulmonary tuberculosis	143 (11.7)	119 (11.2)	24 (14.5)	1.33 (0.83-2.14)	0.233
Miliary tuberculosis	38 (3.1)	31 (2.9)	7 (4.2)	1.46 (0.63-3.37)	0.377
Pleural tuberculosis	31 (2.5)	28 (2.6)	3 (1.8)	0.68 (0.20-2.25)	0.520
Abdominal tuberculosis	27 (2.2)	25 (2.4)	2 (1.2)	0.50 (0.12-2.15)	0.354
Tuberculous meningitis	23 (1.9)	16 (1.5)	7 (4.2)	2.87 (1.16-7.08)	**0.022**
[b] Other	29 (2.4)	23 (2.2)	6 (3.6)	1.69 (0.68-4.21)	0.262
Bacterial pneumonia	276 (22.5)	237 (22.4)	39 (23.4)	1.06 (0.72-1.57)	0.754
Pneumocystis jirovecii pneumonia	47 (3.8)	37 (3.5)	10 (6.0)	1.77 (0.86-3.63)	0.119
Cryptococcal meningitis	39 (3.2)	29 (2.7)	10 (6.0)	2.27 (1.09-4.76)	**0.029**
Bacterial meningitis	30 (2.5)	18 (1.7)	12 (7.2)	4.50 (2.13-9.53)	**0.001**
Acute gastroenteritis	56 (4.6)	51 (4.8)	5 (3.0)	0.61 (0.24-1.56)	0.304
Chronic gastroenteritis	30 (2.5)	28 (2.6)	2 (1.2)	0.45 (0.11-1.90)	0.277
No. of organ systems affected					
1	460 (37.6)	430 (40.6)	30 (18.1)	1.00 (Reference)	
2	432 (35.2)	384 (36.3)	48 (28.9)	1.79 (1.11-2.89)	**0.016**
≥3	332 (27.2)	244 (23.1)	88 (53.0)	5.17 (3.32-8.05)	**<0.001**
qSOFA score					
Low score (0-1 point)	921 (82.5)	823 (85.5)	98 (63.6)	1.00 (Reference)	
High score (2-3 points)	196 (17.5)	140 (14.5)	56 (36.4)	3.35 (2.31-4.88)	**<0.001**
NEWS-2 score					
Low score (0-4 points)	449 (40.2)	415 (43.1)	34 (22.1)	1.00 (Reference)	
[c] Medium score (5-6 points)	171 (15.4)	146 (15.2)	25 (16.2)	2.09 (1.21-3.62)	**0.009**
High score (≥7 points)	496 (44.4)	401 (41.7)	95 (61.7)	2.89 (1.91-4.38)	**<0.001**
Disposition from the ED					
Ward admission	813 (66.5)	712 (67.3)	101 (60.8)	1.00 (Reference)	
ICU admission	205 (16.7)	140 (13.2)	65 (39.2)	3.27 (2.28-4.69)	**<0.001**
Hospital length of stay					
<7 days	830 (67.8)	732 (69.2)	98 (59.0)	1.00 (Reference)	
≥7 days	394 (32.2)	326 (30.8)	68 (41.0)	1.56 (1.11-2.18)	**0.010**

OR – Odds ratio

Bold – denotes statistical significance

[a] Only includes participants with isolated pulmonary tuberculosis

[b] Tuberculous lymphadenitis (n=10), tuberculous pericarditis (n=9), tuberculoma (n=4), urogenital tuberculosis (n=3), spinal tuberculosis (n=2), tuberculous osteomyelitis (n=1)

[c] Includes patients with an overall low score but achieving 3 points in any individual parameter

After adjusting for age and HIV VL and after removing participants with missing data, variables with P < 0.1 from the univariate analysis were subjected to multivariate logistic regression. A total of 869 (71.0%) participants were included in the final model (Table 12). Only respiratory rate > 20 breaths/min (OR = 1.90, P = 0.012), creatinine > 120 mmol/L (OR = 1.97, P = 0.006), oxygen saturation < 90% (OR = 2.09, P = 0.011), white cell count < 4.0 9 10^9/L (OR = 2.09, P = 0.008), ART non-adherence or not yet on ART (OR = 2.39, P = 0.012), GCS < 15 (OR = 2.53, P = 0.000), albumin < 35 g/L (OR = 2.61, P = 0.002), lactate > 2 mmol/L (OR = 4.83, P = 0.000) and cryptococcal meningitis (OR = 6.78, P = 0.000) were significantly associated with in-hospital mortality.

Table 12: Variables significantly associated with in-hospital mortality after subjecting relevant data to multivariate analysis

Parameter	Multivariate analysis	
	OR (95% CI)	**P-value**
[a] ART non-adherent or not yet on ART	**2.39 (1.21-4.74)**	**0.012**
Glasgow coma scale <15	2.54 (1.51-4.27)	**0.000**
Respiratory rate >20 breaths/min	1.90 (1.15-3.13)	**0.012**
Oxygen saturation <90%	2.09 (1.18-3.71)	**0.011**
White cell count <4.0 x 10^9/L	2.09 (1.21-3.60)	**0.008**
Creatinine >120 μmol/L	1.97 (1.22-3.19)	**0.006**
Lactate >2 mmol/L	4.83 (2.91-8.01)	**0.000**
Albumin <35 g/L	2.61 (1.41-4.84)	**0.002**
Cryptococcal meningitis	6.78 (2.52-18.25)	**0.000**

OR – Odds ratio
Model adjusted for age and HIV viral load
[a] Includes all participants that reported ART non-adherence as well as all participants that were not yet initiated on ART prior to presentation

6.5 Discussion

Although many of the variables identified in this study may also be predictors of mortality and severity of illness in patients with other non-HIV-related illnesses (Capuzzo et al., 2000), the combination of variables identified in this study is unique. On univariate analysis of the data, 29 variables were associated with a significantly higher likelihood of in-hospital mortality (male sex, newly diagnosed with HIV, not yet initiated on ART, ART non-adherence, GCS, respiratory rate, systolic blood pressure, oxygen saturation, heart rate, HIV VL, CD4 cell count, haemoglobin, white cell count, platelet count, urea, creatinine, albumin, lactate, CRP, alanine

transaminase, disseminated tuberculosis, tuberculous meningitis, cryptococcal meningitis, bacterial meningitis, number of organ systems affected, qSOFA score, NEWS-2 score, ICU admission and length of hospital admission) and after subjecting the data to multivariate logistic regression, nine variables were found to be associated with a significantly higher likelihood of in-hospital mortality (ART non-adherence or not yet on ART, GCS < 15, respiratory rate > 20 breaths/min, oxygen saturation < 90%, white cell count < 4.0 9 10^9/L, creatinine > 120 mmol/L, albumin < 34 g/L, lactate > 2 mmol/L and cryptococcal meningitis).

To our knowledge, this is the largest and most comprehensive single-centre study to have determined predictors of in-hospital mortality in consecutive HIV-positive patients in an ED setting. Findings pertaining to other aspects of this study have been published separately (Laher et al., 2021). Although multiple studies have reported on the predictive value of various parameters in HIV-positive patients, most of these studies only reported on a few variables and were predominantly conducted in outpatient settings.

In a multicentre study that included data from 12 078 hospitalized HIV-positive patients across 43 hospitals in Portugal over a 3-year period, the risk of hospital mortality was 27% higher in males, with each additional year increase in age being associated with a 1.3% higher risk of in-hospital mortality. Pneumonia and each additional diagnosis were associated with 43% and 2% higher risk of in-hospital mortality, respectively; however, interestingly, tuberculosis was associated with a 22% reduced risk of in-hospital mortality (Dias et al., 2009). In a separate study that reviewed data from 2004 to 2013 and included 95 857 HIV-positive patients in Uganda, significant (P < 0.001) predictors of overall mortality were male sex (OR = 1.37), age > 45 years or age < 25 years (OR = 1.15), unemployment (OR = 1.28), having no schooling (OR = 1.47) or only primary school education (OR = 1.38), CD4 cell count < 100 cells/mm^3 (OR = 3.37) and weight < 45 kg (OR = 2.44) (Rubaihayo et al., 2015). Another study that was conducted in Nepal and included 3799 HIV-positive adult patients who were identified from the national ART register found that baseline predictors of mortality were male gender [adjusted hazard ratio (aHR) = 2.08], clinical stage III (aHR = 1.67) or IV (aHR = 2.21) disease, lower body weight (aHR = 1.04) and CD4 cell count < 150 cells/mm^3 (aHR = 2.14) (Angdembe et al., 2019). Furthermore, in a systematic review that included 17 studies, all of which were conducted

in Ethiopia and comprised 19 321 pooled HIV-positive patients on ART, the following were identified as predictors of mortality: CD4 < 50 cells/mm^3 at ART initiation (aHR: 1.8–4.5), HIV stage III and IV disease (aHR: 1.4–11.2), poor treatment adherence (aHR: 2.1–27.8), low baseline haemoglobin level (aHR: 1.9–5.5), co-infection with tuberculosis (aHR: 1.3–4.5) and poor functional status (aHR: 2.4–6.9) (Biset Ayalew, 2017). Comparatively, in our study, on univariate analysis the likelihood of in-hospital mortality was 1.49 times higher in males and 5.17 times higher in participants presenting with ≥ 3 organ system pathology, and there were no significant differences with regard to age and bacterial pneumonia. Although tuberculosis, in general, was not associated with a higher likelihood of in-hospital mortality, disseminated tuberculosis (OR = 1.98) and tuberculous meningitis (OR = 2.87) were associated with a higher likelihood of in-hospital mortality in this study. Not surprisingly, and in keeping with previous studies (Jarvis et al., 2014; Wall et al., 2013), bacterial meningitis (OR = 4.50) on univariate analysis and cryptococcal meningitis on univariate (OR = 2.27) as well as multivariate (OR = 6.78) analysis were each also associated with a significantly higher likelihood of in-hospital mortality.

With regard to haematological parameters, in this study leukopenia was independently associated with a two-fold higher likelihood of in-hospital mortality, while anaemia (OR = 1.63) and thrombocytopenia (OR = 3.04) were only associated with a higher likelihood of in-hospital mortality on univariate analysis. Anaemia as a predictor of worse outcomes has been described in a number of studies. In a study conducted in Tanzania that enrolled 320 treatment-naive adults at ART initiation who were followed up for a median duration of 10.9 months, independent predictors of mortality were haemoglobin < 8 g/dL (aHR = 9.20), haemoglobin 8–9.9 g/dL (aHR = 7.50), haemoglobin 10–11.9 g/dL (AHR = 4.03), thrombocytopenia (aHR = 2.30) and lymphopenia (aHR = 1.72) (Johannessen et al., 2008). Another study demonstrated that every 1 g/dL decrease in haemoglobin was independently associated with a 57% increase in mortality (Mocroft et al., 1999). In a cohort study that included 1350 adults who had been initiated on ART across 27 clinics in South Africa, the aHR for mortality with haemoglobin < 8 and 8.1–9.9 g/dL were 4.99 and 3.05, respectively (Russell et al., 2010). In the Multistate Adult and Adolescent Spectrum of HIV Disease Surveillance Project that retrospectively reviewed the medical charts of 32 867 HIV-positive patients, mortality was significantly higher in patients

with anaemia, with a 56% increase in the risk of death in anaemic patients with a baseline CD4 cell count < 200 cells/mm^3 (Sullivan et al., 1998). In contrast to the studies described, our study differed in that it was conducted in acutely ill HIV-positive patients in the ED.

Similar to the findings of this study, where CRP > 100 mmol/L was associated with a 3.3-fold higher likelihood of in-hospital mortality, other studies have also found CRP to be a predictor of HIV progression and mortality. However, many of these studies did not exclusively include patients presenting with an acute illness. In a multicentre study that comprised 513 HIV-positive men, the degree of CRP elevation was associated with HIV disease progression, which was independent of the CD4 cell count and HIV VL (Lau, 2006). In another study, after adjusting for age, body mass index, albumin, CD4 cell count and HIV VL, CRP was found to be a predictor of mortality, with the increased risk varying from 3.4- to 13.6-fold depending on the degree of CRP elevation (Feldman et al., 2003). A study conducted in Tanzania reported that a high maternal CRP independently predicted maternal as well as child mortality (Drain et al., 2007).

In this study, hypalbuminaemia was associated with a significantly higher likelihood of in-hospital mortality, with lower levels (< 25 g/L) being associated with an even higher likelihood of in-hospital mortality. In a study that measured the albumin concentration at ART initiation in 2145 adults, patients with an albumin concentration < 35 g/L had a 4.52-fold higher risk of death after multivariate adjustment (Sudfeld et al., 2013). In a multi-institutional study comprising 2056 HIV-infected women at various stages of HIV disease, the aHR for mortality was 3.1 times higher ($P < 0.01$) in patients with albumin < 35 g/L, after adjusting for CD4 cell count, HIV VL, haematocrit level, age and body mass index (Feldman et al., 2000). Another study reported that HIV-positive patients with an albumin < 25 g/L had a three-fold higher risk of mortality (Lang et al., 2013). Again, these studies investigated the predictive value of albumin in relation to long-term mortality and not in the context of acute in-hospital mortality, as was investigated in this study.

In this study, on both univariate and multivariate analysis, hyperlactataemia was associated with a significantly higher likelihood of in-hospital mortality, with higher levels (>5 mmol/L) associated with an extremely high likelihood of mortality on univariate analysis. While the

causes of hyperlactataemia in HIV-positive patients may be manifold (Tantisiriwat et al., 2001), previous studies predominantly reported on hyperlactataemia secondary to the use of the older-generation nucleoside reverse transcriptase inhibitor class of ART. In a study that examined this as a cause, the prevalence rates of hyperlactataemia in HIV-positive patients receiving ART and in patients not on ART were 18.7% and 6.7%, respectively (Mamiafo et al., 2014). With the introduction of safer ART treatment regimens in the past few years, however, the incidence of ART-induced lactic acidosis has significantly declined ("HIV and Lactic Acidosis," 2020). In acutely ill patients in general, hyperlactataemia has been shown to predict mortality independently (Khosravani et al., 2009). In one such study, blood lactate levels > 5 mmol/L were associated with an 80% mortality rate (Stacpoole et al., 1994). As such, lactate levels may be a useful marker in HIV-positive patients with an acute illness.

While many of the parameters discussed have been shown to be independent predictors of mortality in this or previous studies (as discussed earlier), it is likely that the concurrent presence of more than one of these parameters in a single patient may be associated with higher rates of mortality. Hence, the development of a scoring tool comprising several of these outcome predictive parameters may help clinicians to better classify disease severity and prognostication, as well as guide appropriate clinical management and the use of limited resources.

6.6 Limitations

Among the limitations of this study is the fact that it was a single-centre study that focused on in-hospital mortality. Hence, patients were not followed up after hospital discharge, and therefore long-term mortality was not determined. Furthermore, as the study was conducted at a tertiary-level academic hospital and, therefore, patients with less severe presenting illnesses were triaged to a lower level of care facility, our cumulative findings are likely to be overestimated and may not be fully reflective of the actual dynamics of the HIV-positive population residing within the drainage area of the hospital.

6.7 Conclusions

Routine clinical and laboratory parameters are useful in predicting in-hospital mortality in HIV-positive patients presenting to the ED with an acute illness. These parameters may be of value in

guiding clinical decision-making, directing the appropriate use of resources, and influencing patient disposition, and they may also be useful in developing an outcome prediction tool for use in HIV-positive patients in the ED. Interventions such as the prescription of empirical antibiotics, rapid induction of ART and other mechanisms to reduce this mortality need to be evaluated in appropriately conducted clinical trials.

Acknowledgements

The authors would like to thank the staff at the Charlotte Maxeke Johannesburg Academic Hospital for their assistance with identifying potential study participants.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

A.E.L. was the primary author and was responsible for the study design, data collection, data analysis, manuscript write-up, revision, and approval of the final manuscript. W.D.F.V., G.A.R. and F.P. assisted with the study design, interpretation of results, revision of the manuscript and approval of the final manuscript.

Funding information

This research was self-funded and did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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CHAPTER 7: ARTICLE 5

The manuscript was published in the journal *HIV Medicine* on 05 January 2022: doi:10.1111/hiv.13159. The journal is indexed in PubMed, Web of Science (Impact Factor 3.55) and Scopus (CiteScore 5.8).

Development and internal validation of the HIV In-hospital Mortality Prediction (HIV-IMP) risk score

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7.1 Abstract

Background: Despite advances in availability and access to antiretroviral therapy (ART), HIV still ranks as a major cause of global mortality.

Objectives: The aim of this study was to develop and internally validate a risk score capable of accurately predicting in-hospital mortality in HIV-positive patients requiring hospital admission.
Methods: Consecutive HIV-positive patients presenting to the Charlotte Maxeke Johannesburg Academic Hospital adult emergency department between 7 July 2017 and 18 October 2018 were prospectively enrolled. Multivariate logistic regression was used to determine parameters for inclusion in the final risk score. Discrimination and calibration were assessed by means of the area under the receiver operating curve (AUROC) and the Hosmer–Lemeshow goodness-of-fit test, respectively. Internal validation was conducted using the regular bootstrap technique.
Results: The overall in-hospital mortality rate was 13.6% (n = 166). Eight predictors were included in the final risk score: ART non-adherence or not yet on ART, Glasgow Coma Scale < 15, respiratory rate > 20 breaths/min, oxygen saturation < 90%, white cell count < 4 × 109/L, creatinine > 120 μmol/L, lactate > 2 mmol/L and albumin < 35 g/L. After internal validation, the risk score maintained good discrimination [AUROC 0.83, 95% confidence interval (CI): 0.78–0.88] and calibration (Hosmer–Lemeshow $\chi^2 = 2.26$, $p = 0.895$).
Conclusion: The HIV In-hospital Mortality Prediction (HIV-IMP) risk score has overall good discrimination and calibration and is relatively easy to use. Further studies should be aimed at externally validating the score in varying clinical settings.

Keywords
AUROC, calibration, discrimination, HIV, in-hospital mortality, internal validation, outcome prediction score

7.2 Introduction

The widespread availability of safer regimens of antiretroviral therapy (ART) over recent years has resulted in a substantial reduction in HIV-related morbidity and mortality (Trickey et al., 2017). Despite this, the global burden of HIV remains high, with HIV currently ranking as the third highest cause of global mortality after cardiovascular disease and cancer ("Top 10 leading causes of death in the world from 1990-2019 complete ranking," 2019). In 2019, there were approximately 1.7 million new cases of HIV with 690 000 HIV-related deaths ("UNAIDS Data 2020," 2020).

Even in regions with high rates of ART coverage, HIV-related hospital admissions and deaths remain disproportionately high (Barak et al., 2019). In addition, the cost of hospitalization due to an acute HIV-related illness is a major contributor to the overall financial burden of the disease (Barbour et al., 2009; Jones et al., 2019). Hence, identifying factors that are associated with unfavourable outcomes in HIV-positive patients requiring hospitalization may be useful in guiding clinical decision-making, directing the allocation of scarce resources, and influencing patient disposition.

Outcome prediction scores or models are clinical tools that are designed to assist healthcare professionals with reasonably predicting patient outcomes (Shipe et al., 2019). Many such models have previously been developed and validated in various disciplines of clinical medicine (Deppen et al., 2014; Knaus et al., 1985; Vincent et al., 1996). Although previous prediction tools have been developed for use in people living with HIV (PLWH), these predominantly focused on predicting the virological response to ART and other specifics relating to HIV presentation (Friis-Møller et al., 2016; Heider et al., 2014; Wang et al., 2009). However, there are currently no models that are able to predict mortality in HIV-positive patients requiring hospital admission. Hence, the aim of this study was to develop and internally validate a risk score that will be capable of accurately predicting in-hospital mortality in HIV-positive patients requiring hospital admission.

7.3 Methods

Study setting

The study was conducted at the adult medical emergency department (ED) unit of the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). The CMJAH is a 1088-bed tertiary-level academic hospital that is affiliated to the University of the Witwatersrand. The adult medical ED unit manages all non-trauma patients who are ≥ 16 years old. Upon presentation to the triage section of the ED, patients are briefly assessed and thereafter categorized into one of four triage categories – ‘emergent’ (red), ‘very urgent’ (orange), ‘urgent’ (yellow) or ‘routine’ (green) – based on specific criteria as defined by the SA Triage Scale (Bruijns et al., 2008). As CMJAH is a tertiary-level facility, in general patients who are categorized as red, orange, or yellow are managed at the facility, while more stable patients who are categorized as green are referred to

an alternate facility for further care. Additionally, clinically stable patients not residing within the drainage area of the facility are also referred to an alternate facility closer to the patient's residence.

HIV testing protocol at the study site

As per the facility protocol, excepting patients who are known to be HIV-positive (either self-reported or based on past laboratory records), all other patients attending the ED are first counselled and thereafter encouraged to undergo in-unit rapid HIV testing to determine their HIV status. Whole blood samples of patients consenting to HIV testing are subjected to diagnostic testing with the Abon HIV 1/2/0 Tri-line Rapid test (Abon Biopharm, Hangzhou, RR China). Reactive samples are thereafter subjected to a second confirmatory rapid test (First Response HIV 1–2.0 card; PMC Medical India Pvt, Ltd, Daman, India). In those in whom the first test is positive, but the confirmatory test is negative, a sample of whole blood is collected and sent to the laboratory for HIV enzyme-linked immunosorbent assay testing.

Inclusion criteria, exclusion criteria and primary outcome measure

Adult patients ≥ 18 years who previously tested positive for HIV as well as those who were newly diagnosed with HIV after ED presentation were prospectively enrolled into the study between 7 July 2017 and 18 October 2018. This included HIV-positive patients who required admission as well as patients who were discharged from the ED but excluded patients who were referred to another facility from the triage area. In addition, HIV-negative patients, HIV-status-unknown patients not consenting to HIV testing as well as patients not consenting to study participation were excluded. The primary outcome measure of the study was in-hospital mortality, which we defined as death occurring at any time during hospital admission.

Data collection

Data collection commenced once ethics clearance (University of the Witwatersrand Human Research Ethics Committee- clearance certificate number M160512) and the relevant permissions were obtained. Prior to the commencement of data collection, informal training pertaining to the methodology and principles of data collection from medical charts was undertaken by the primary investigator. After briefing all doctors employed in the ED regarding

commencement of data collection, informal training pertaining to the methods and principles of data collection from medical charts was undertaken by the primary investigator. After briefing all doctors employed at the ED about the study aim, objectives and design, doctors were requested to inform the primary investigator of any HIV-positive patients being managed in the ED. Written informed consent for study participation was obtained from potential participants by either the primary investigator or the doctor on shift. In the event that participants were unable to grant consent (e.g., decreased level of consciousness), consent was obtained from the next of kin/legal guardian and later re-obtained from the participant in the event that there was an improvement in mental capacity. The ED registers were also reviewed daily in an effort to identify potential participants who may have been missed by the ED doctors.

The four question AIDS Clinical Trials Group Adherence Questionnaire (ACTG-AQ) was utilized to determine non-adherence to ART (Chesney et al., 2000). Those who responded 'yes' to any of the questions were regarded as being ART-non-adherent. The questionnaire was administered to all participants who had been prescribed ART at any time in the past.

Data were extracted from the patient's hospital file by the primary investigator and thereafter captured into an anonymized and standardized data collection form that was created in the RedCap system (Harris et al., 2009). Additional information relevant to the study but not found in the patient's hospital records was directly obtained from the participant, the participant's laboratory records, or the participant's next of kin/legal guardian where applicable. Only where the next of kin/legal guardian indicated that they were aware of the participant's HIV status, were they questioned regarding relevant HIV history, such as treatment adherence. Data from hospital records were collected over the entire duration of hospital stay or until data collection was completed. Inter-rater reliability was assessed by an independent researcher experienced in the methods of data collection but blinded to the study's aim and objectives. To assess this, data extracted from a random sample of 43 medical charts were compared with data extracted by the primary investigator.

Data relevant to this study included demographic details (age, sex and marital status), whether participants were newly or previously diagnosed with HIV, ART non-adherence, whether ART

was initiated prior to ED attendance, vital signs at ED arrival [Glasgow Coma Scale (GCS) score, respiratory rate, systolic blood pressure, oxygen saturation and heart rate] and laboratory findings at presentation [CD4 cell count, HIV viral load (VL), haemoglobin, white cell count, platelet count, urea, creatinine, albumin, lactate, C-reactive protein (CRP) and alanine transaminase]. The data were thereafter exported to Microsoft Excel (Microsoft 365, v.16.0.13029.20232) and subsequently to Stata v.16 (StataCorp Ltd, College Station, TX, USA) for statistical analysis. Although data pertaining to vital signs and laboratory parameters were collected as continuous variables, these were reported as categorical variables based on cut-offs that are commonly regarded as clinically significant (e.g., CD4 cell count < 100 cells/μL; albumin < 35 g/L etc.). Study reporting was in conformance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (Elm et al., 2007).

Risk score development

Selection of predictor variables

In developing the HIV In-hospital Mortality Prediction (HIV-IMP) score, we initially determined which factors were associated with a higher likelihood of in-hospital mortality. Hence, we first subjected relevant data to univariate and thereafter multivariate logistic regression analysis. In the univariate analysis, for each variable assessed by means of binary logistic regression, all available case information was utilized. Variables from the univariate analysis with a p-value < 0.1 were thereafter subjected to multivariate analysis. Patients with missing data pertaining to variables that were included in the multivariate analysis were dropped from the model. Thereafter, through the process of stepwise backward regression, non-significant variables were dropped until the final risk score was achieved. Variables from the multivariate logistic regression analysis with a two-sided p-value < 0.05 (independent predictors of in-hospital mortality) were selected for inclusion in the predictive risk score. Crude odds ratio (OR) with 95% confidence interval (CI) were reported for parameters included in the univariate and multivariate analyses.

Each of the independent predictors were thereafter assessed to create a scoring system. The weighting score allocated to each of the independent variables was based on the regression coefficient (β) for that variable, where variables with $\beta < 1$ were assigned a score of 1 point and

variables with β in the range 1–2 were assigned a score of 2 points. Weighting scores were assigned to each study participant for each of the included variables. For variables that were outside the defined cut-off range (e.g., oxygen saturation ≥ 90%, albumin ≥ 35 g/L, etc.), a weighting score of zero was allocated. The final risk score for each participant was calculated by summing up the weighting scores achieved for each of the included variables. Hence, the minimum achievable risk score was 0 and the maximum was 10 points.

Evaluating the performance of the model

Various approaches were implemented to evaluate the performance of the risk score. First, to determine whether higher risk scores were associated with higher rates of in-hospital mortality, we calculated and tabulated the actual rate of in-hospital mortality for the entire range of risk scores (0–10) achieved by the study population on whom the risk score was developed. Second, we plotted the relationship between the approximate predicted probability of in-hospital mortality and the risk score. Thereafter, we evaluated discrimination and calibration of the risk score on the entire study sample prior to subjecting it to internal validation.

Discrimination refers to the ability of a risk score or model to distinguish between patients with the outcome (in-hospital mortality) from those without the outcome and can be quantified with measures such as sensitivity and specificity. We assessed discrimination using the area under the receiver operating characteristic curve (AUROC) (also known as the C statistic), which plots the sensitivity (true positive rate) against 1 –specificity (false-positive rate) for consecutive cut-offs for the probability of an outcome. While an AUROC of 0.5 implies that the model is worthless (true-positive rate = false-positive rate), an AUROC > 0.8 implies good accuracy and an AUROC > 0.9 implies very good accuracy of a model (Laher et al., 2017; Obuchowski, 2003).

Calibration refers to the agreement between observed outcomes and expected outcomes (predictions) (Alba et al., 2017). For example, if we predict a 20% risk of in-hospital mortality in HIV-positive patients admitted from the ED, the observed frequency of in-hospital mortality should be approximately 20 out of 100 patients. We assessed calibration using the Hosmer–Lemeshow goodness-of-fit test for logistic regression. The frequency of observed and expected outcomes were divided into 10 deciles of predictive index, with each corresponding to a defined

probability of in-hospital mortality. Therefore, in the context of this study, the test was used to determine whether differences between observed and expected probabilities of in-hospital mortality were non-significant, thereby indicating acceptable model fit. Hence, a lower χ^2 statistic with a higher (non-significant) p-value is indicative of a better-fitting model and good calibration (Hosmer and Lemesbow, 1980). A limitation of the Hosmer–Lemeshow test is that it does not give an indication of the magnitude of the difference or whether there is variation among patients with high versus low risk of the outcome (Alba et al., 2017).

Internal validation refers to the performance of the model in patients from a similar population to which the sample originated. The bootstrap technique with correction for optimism in risk score performance (optimism-corrected bootstrapping) was used to internally validate the risk score that was developed. Bootstrapping is the process of random sampling with replacement from an original dataset for use in obtaining statistical inference (Efron, 1983; Efron and Tibshirani, 1997; Steyerberg et al., 2001). Optimism is a form of bias that may occur when fixing a model to the same data that were used for testing. The difference between the apparent performance, which estimates the performance in the bootstrap sample, and the test performance, which estimates the performance in the original sample, is an estimate of the optimism in the apparent performance (Steyerberg et al., 2001). In this study, the predictive risk score, which was developed from the entire original sample, was applied to each of 200 bootstrap samples that were randomly drawn with replacement from the original study sample with each bootstrap sample comprising approximately 70% (≈ 670) of the original study sample. Discrimination (AUROC) and calibration (Hosmer–Lemeshow χ^2 statistic and p-value) were determined for each bootstrap sample, whereafter optimism and the optimism-corrected average AUROC and $\chi 2$ statistic with p-value for the entire risk score were determined and reported.

7.4 Results

Of the 29 416 patients that presented to the triage area of the adult medical ED over the period of data collection, 11 383 were triaged into the ED for further management while the remainder were referred to an appropriate facility, in accordance with the CMJAH ED triage protocol. A total of 1308 patients were HIV-positive, of whom 84 were excluded from the study as informed consent could not be obtained; hence, the final study sample comprised 1224 patients. The in-

hospital mortality rate was 13.6% (n = 166). Clinical characteristics of study patients with univariate logistic regression analysis to determine factors that were associated with a higher likelihood of in-hospital are described in Table 13.

Model development

Nineteen of the 21 variables that were analysed by means of univariate regression analysis were associated with a significantly higher likelihood of in-hospital mortality (Table 13). Lactate >2 mmol/L (OR 5.41, 95% CI 3.69-7.95, p<0.001), albumin <35 g/L (OR 4.34, 95% CI 2.66-7.11, p<0.001) and GCS <15 (OR 3.66, 95% CI 2.55-5.26, p <0.001) displayed the highest ORs.

Table 13: Clinical characteristics of study patients with univariate logistic regression to determine factors associated with a higher likelihood of in-hospital mortality

	Survival to discharge (n, %)	**In-hospital mortality (n, %)**	**OR (95% CI)**	**P-value**
Age (years) [median (IQR)]	36 (31-44)	38 (30-45)	1.01 (0.99-1.02)	0.328
Male sex	462 (43.7)	89 (53.6)	1.49 (1.07-2.07)	**0.017**
Married	240 (22.7)	47 (28.3)	1.35 (0.93-1.94)	0.112
Newly diagnosed HIV	167 (15.8)	45 (27.1)	1.98 (1.36-2.90)	**<0.001**
ART non-adherence or not yet on ART	592 (56.0)	116 (69.9)	1.83 (1.28-2.60)	**0.001**
Respiratory rate >20 breaths/min	349 (36.2)	85 (55.2)	2.17 (1.54-3.06)	**<0.001**
Oxygen saturation <90%	157 (16.3)	39 (25.3)	1.74 (1.16-2.6)	**0.007**
Systolic blood pressure <90 mmHg	91 (9.4)	25 (16.2)	1.86 (1.15-3.00)	**0.011**
Heart rate >110 beats/min	473 (49.1)	92 (59.7))	1.54 (1.09-2.17)	**0.015**
Glasgow coma scale <15	157 (18.8)	64 (68.8)	3.66 (2.55-5.26)	**<0.001**
CD4 <100 cell/mm^3	433 (44.8)	94 (67.6)	2.58 (1.77-3.76)	**<0.001**
HIV viral load >1000 copies/mL	537 (58.1)	82 (65.6)	3.16 (2.15-4.65)	**<0.001**
Haemoglobin <11 g/dL	484 (49.7)	95 (61.7)	1.63 (1.15-2.31)	**0.006**
White cell count <4 x 10^9/L	137 (14.1)	33 (21.6)	1.68 (1.10-2.57)	**0.017**
Platelet count <150 x 10^9/L	165 (17.0)	58 (38.4)	3.04 (2.11-4.40)	**<0.001**
Urea >10 mmol/L	205 (22.2)	72 (49.3)	3.41 (2.38-4.88)	**<0.001**
Creatinine >120 μmol/L	225 (24.8)	73 (50.0)	3.06 (2.14-4.37)	**<0.001**
C-reactive protein >100 mg/L	417 (45.6)	99 (68.3)	3.30 (1.72-6.32)	**<0.001**
Lactate >2 mmol/L	349 (36.4)	121 (75.6)	5.41 (3.69-7.95)	**<0.001**
Albumin <35 g/L	518 (57.2)	116 (85.2)	4.34 (2.66-7.11)	**<0.001**
Alanine transaminase >100 mmol/L	80 (9.0)	29 (20.9)	2.67 (1.67-4.27)	**<0.001**

ART – antiretroviral therapy, CI – confidence interval, OR – Odds ratio

After adjusting for age and HIV VL, variables from the univariate regression analysis with a p-value <0.1 were thereafter subjected to multivariate regression analysis. The final risk score comprised 958 (78.3%) study participants with complete data for the included variables. Table 14 describes the eight variables that were associated with a significantly higher likelihood of in-hospital mortality after multivariate regression analysis and were hence selected for inclusion in the predictive risk score along with their respective regression coefficient (β), odds ratio, 95% CI, p-value, and allocated weighting toward the risk score. The process as to how weighting scores for each variable and the final risk score was determined is described in the "Methods" section.

Table 14: Variables associated with a significantly higher likelihood of in-hospital mortality on multivariate analysis, along with the associated regression coefficient (β), odds ratio, 95% CI, p-value, and allocated weighting score

Parameter	β	OR (95% CI)	P-value	Weighting score
ART non-adherent or not yet on ART	0.75	2.12 (1.30-3.43)	0.002	1
Glasgow coma scale <15	1.17	3.23 (1.99-5.24)	<0.001	2
Respiratory rate >20 breaths per minute	0.46	1.59 (1.01-2.51)	0.045	1
Oxygen saturation <90%	0.78	2.19 (1.28-3.74)	0.004	1
White cell count <4 x 10^9/L	0.65	1.92 (1.14-3.24)	0.014	1
Creatinine >120 μmol/L	0.70	2.02 (1.29-3.15)	0.002	1
Lactate >2 mmol/L	1.62	5.05 (3.15-8.11)	<0.001	2
Albumin <35 g/L	0.86	2.37 (1.36-4.14)	0.002	1

ART – antiretroviral therapy

Performance of the model

Actual rates of in-hospital mortality

Actual rates of in-hospital mortality for the entire range of risk scores achieved by the cohort of 958 study participants on whom the predictive risk score was developed is described in table 15. It is notable that every unit increase in risk score was associated with a higher rate of in-hospital mortality.

Probability of in-hospital mortality

The relationship between the risk score achieved among study participants and their approximate predicted probability of in-hospital mortality is plotted in figure 8. Notably, the distribution

points suggest a positive relationship between the two, i.e., the higher the risk score, the higher the predicted probability of in-hospital mortality. For example, if a patient has a risk score of 7, the probability (95% CI) of in-hospital mortality is 46.67% (42.82-50.51) and if a patient has a risk score of 8, the probability (95% CI) of in-hospital mortality is 64.12% (62.36-65.89).

Table 15: Actual rates of in-hospital mortality for the entire range of risk scores achieved by the cohort of study participants on whom the model was derived

Total score	Survival to discharge (n=806)	In-hospital mortality (n=152)	In-hospital mortality rate (%)
0	80	0	0
1	111	2	1.8
2	142	8	5.4
3	154	9	5.5
4	139	27	16.3
5	106	36	25.3
6	48	30	38.4
7	16	18	52.9
8	9	17	65.4
9	1	4	80.0
10	0	1	100

Assessing discrimination and calibration of the model

After applying the predictive risk score to the study cohort, the estimated AUROC (figure 9) was 0.83 (95% CI 0.78 – 0.86), indicating good discriminative ability of the risk score. The Hosmer–Lemeshow goodness-of-fit test describing the probability of in-hospital mortality in each decile of predictive index and their associated frequency of outcomes are given in table 16. Notably, the expected and observed number of participants with in-hospital mortality in each decile of the predictive index were similar, with their being only slight over- or under-fit in deciles 1-9 and perfect fit of the risk score in decile 10. The χ^2 estimate was 4.05 ($p = 0.853$) indicating acceptable calibration of the HIV-IMP risk score.

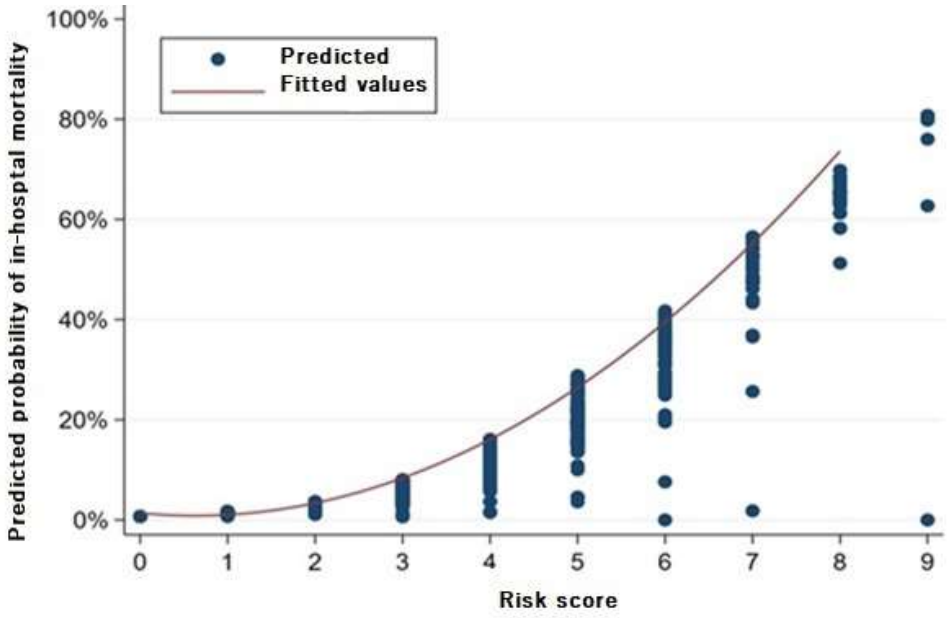


Figure 8: Relationship between the HIV In-hospital Mortality Prediction (HIV-IMP) risk score and predicted probability of in-hospital mortality

Risk score and associated probability of in-hospital mortality (95% confidence interval) – risk score = 0: 0.72 (0.72-0.74); risk score = 1: 1.45 (1.41-1.49); risk score = 2: 2.91 (2.81-3.01); score = risk 3: 5.70 (5.49-5.92); risk score = 4: 11.67 (11.26-12.08); risk score = 5: 20.41 (19.63-21.18); risk score = 6: 32.79 (31.16-34.42); risk score = 7: 46.67 (42.82-50.51); risk score = 8: 64.12 (62.36-65.89); risk score ≥ 9: 67.33 (42.00-96.68)

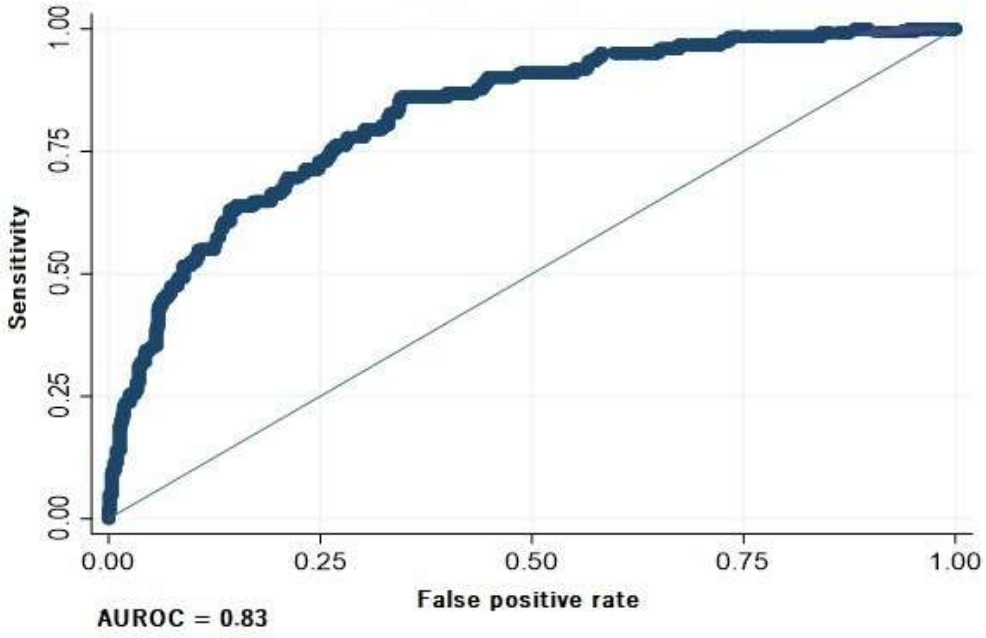


Figure 9: Receiver operating characteristic curve of the prediction model

Table 16: Hosmer-Lemeshow goodness of fit test describing the probability of in-hospital mortality for each decile of predictive index and their associated frequency of outcomes

Decile of Predictive Index	Probability of in-hospital mortality	Observed in-hospital mortality (n)	Expected in-hospital mortality (n)	Observed survival (n)	Expected survival (n)	Total observed (n)
1	0.012	0	0.7	96	95.3	96
2	0.017	2	1.4	94	94.6	96
3	0.032	3	2.2	93	93.8	96
4	0.047	5	3.5	91	92.5	96
5	0.068	4	5.4	91	89.6	95
6	0.105	7	8.0	89	88.0	96
7	0.150	14	12.0	82	84.0	96
8	0.215	13	16.7	83	79.3	96
9	0.348	27	25.1	69	70.9	96
10	0.807	47	47.0	48	48.0	95

$\chi^2 = 4.05$, $p = 0.853$

Internal validation of the model

Internal validation of the model was assessed by estimating the AUROC for each of 200 bootstrap samples [each sample comprised approximately 70% (≈ 670) of the study sample]. The pooled average optimism for the AUROC was 0.006 (95% CI: −0.04–0.05) while the optimism-corrected average AUROC was 0.832, with a tight distribution between samples (95% CI: 0.78–0.88), indicating that the discriminative ability of the risk score did not change appreciably between bootstrap samples. After applying the Hosmer–Lemeshow goodness-of-fit test to each of the 200 bootstrap samples, the average estimated $\chi 2$ was 2.26 ($p = 0.895$), indicating good overall calibration of the risk score.

7.5 Discussion

Despite 30 years having passed since the HIV epidemic began, and with HIV still ranking as one of the leading causes of global mortality ("Top 10 leading causes of death in the world from 1990-2019 complete ranking," 2019), the HIV-IMP score is the first outcome prediction score to have been developed and internally validated for use in HIV-positive patients requiring hospital admission. Findings relating to other aspects of this study, including a discussion pertaining to the predictors of in-hospital mortality reported in this article, have been published elsewhere (Laher et al., 2021a; Laher et al., 2021b, Laher et al., 2021c, Laher et al., 2021d).

The risk score is relatively simple to use and comprises only eight predictor variables, four of which are non-laboratory-based (ART non-adherent or not yet on ART, GCS < 15, respiratory rate > 20 breaths/min and oxygen saturation < 90%) that can easily be acquired within minutes of the patient's arrival to the ED, while the remaining four variables can be considered routine laboratory investigations (white cell count < 4 × 109/L, creatinine > 120 μmol/L, lactate > 2 mmol/L and albumin < 35 g/L) where results may be available within a few minutes of drawing the blood sample in facilities that have access to in-unit point-of-care (POC) testing. It is hoped that the HIV-IMP risk score will positively contribute to the timely and appropriate management of acutely ill HIV-positive patients requiring hospital admission.

With regard to evaluation of the performance of the risk score, various methods have been described to estimate internal validity of predictive logistic regression models. In a study that compared three different methods of internal validation, the authors concluded that performance of both the split-sample and cross-validation methods were suboptimal compared with the bootstrap method (Steyerberg et al., 2001). Hence, in this study we utilized the regular bootstrap method to internally validate our risk score. After subjecting the risk score to bootstrapping, it retained good discrimination (AUROC = 0.83, 95% CI: 0.78–0.88) and calibration (Hosmer–Lemeshow $\chi^2 = 2.26$, p = 0.895). However, prior to implementation in clinical practice, the risk score must be subjected to external validation in other population groups and varying clinical settings.

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to predict in-hospital mortality in intensive care unit (ICU) patients. The model includes 14 variables that relate to age, underlying organ dysfunction, temperature, blood pressure, heart rate, respiratory rate, oxygen saturation, pH, sodium, potassium, creatinine, haematocrit, white cell count and GCS (Knaus et al., 1985). In 1996, Vincent et al. developed the Sepsis-related Organ

Failure Assessment (SOFA) score that also aimed at predicting in-hospital mortality in ICU patients. The model included six variables relating to oxygenation, GCS, blood pressure, bilirubin, platelet count and creatinine. (Vincent et al., 1996). The quick SOFA (qSOFA) score was developed in 2016 by Seymour et al. and aimed to predict in-hospital mortality as well as ICU length of stay in patients presenting to the ED with sepsis. The model comprises three variables that include blood pressure, respiratory rate and GCS (Seymour et al., 2016). Comparatively, the HIV-IMP risk score was developed in HIV-positive patients presenting to the ED with an acute illness with the aim of predicting in-hospital mortality and comprises eight variables, five of which are also included in the models described earlier and which predominantly relate to the acuity of presenting illness (GCS, respiratory rate, oxygen saturation, white cell count and creatinine). Of the three remaining variables, lactate also relates to the acuity of presenting illness while ART non-adherence or not yet on ART and albumin predominantly relate to HIV disease control and chronicity. In a study that investigated outcomes in HIV-positive patients admitted to a tertiary-level hospital ICU, the APACHE II score was shown to overestimate mortality by approximately two-fold (Maphula et al., 2020).

Similar to this study, previous studies conducted in the HIV population also reported poor ART treatment adherence (Biset Ayalew, 2017), leukopenia (Johannessen et al., 2008), renal dysfunction (Kopp, 2011) and hypalbuminaemia (Feldman et al., 2000; Sudfeld et al., 2013) as independent predictors of mortality. These and other studies also reported other variables such as male sex (Angdembe et al., 2019; Rubaihayo et al., 2015), age (Rubaihayo et al., 2015), low CD4 cell count (Angdembe et al., 2019; Biset Ayalew, 2017; Rubaihayo et al., 2015), anaemia (Biset Ayalew, 2017; Johannessen et al., 2008), thrombocytopaenia (Johannessen et al., 2008) and low CRP (Feldman et al., 2003) as independent predictors of mortality. In this study, these additional factors were significantly associated with in-hospital mortality on univariate regression analysis but not multivariate regression analysis. Furthermore, most of these studies were conducted at outpatient settings and did not specifically investigate in-hospital mortality. With regards to other independent predictors of in-hospital mortality that we had identified, tachypnoea (Singla et al., 2021), hypoxia (Sunde et al., 2017) and hyperlactataemia (Khosravani et al., 2009) have been reported as predictors of mortality in the general population but not specifically in the HIV-positive population.

7.6 Limitations

limitation of this study is that it was a single-centre study and as patient outcomes may have been influenced by resource availability, clinical management protocols and clinician expertise at the study site, our findings may differ from that of other facilities. Hence, there is a need to externally validate the risk score prior to clinical use. Another limitation is that we did not account for terminally ill patients who may have been discharged for home-based palliative care, some of whom may have died at home shortly thereafter. Also, when determining the cut-offs for variables such as respiratory rate > 20 breaths/min and GCS < 15, we did not account for younger patients who may present with relatively normal vital signs prior to sudden decompensation. A possible limitation to the implementation of the developed risk score in low and middle-income settings is that some of the laboratory-based variables may not be readily available.

7.7 Conclusion

The HIV-IMP risk score for predicting in-hospital mortality in HIV-positive patients requiring hospital admission has overall good discrimination and calibration and is relatively easy to use. The risk score may be useful in guiding clinical decision-making, directing the allocation of scarce resources, and influencing patient disposition. Further studies should be aimed at externally validating the risk score in varying clinical settings.

Acknowledgements

The authors would like to thank the staff at the Charlotte Maxeke Johannesburg Academic Hospital for their assistance with identifying potential study participants.

Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

AEL: primary author and was responsible for the study design, data collection, data analysis, interpretation of results, manuscript write-up, revision, and approval of the final manuscript. FP, WV, FM, MM & GAR: assisted with the study design, interpretation of the results, revision of the manuscript and approval of the final manuscript. OAA: assisted with statistical analysis, interpretation of the results and approval of the final manuscript.

Funding information

This research was self-funded and did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

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CHAPTER 8: INTEGRATED DISCUSSION, STUDY LIMITATIONS AND STUDY CONCLUSIONS

8.1 Discussion

Although three decades of the HIV epidemic have elapsed, with over 1.3 million deaths to date and HIV having been ranked as the number one cause of global mortality from the year 2003 until 2009 ("Top 10 leading causes of death in the world from 1990-2019 complete ranking," 2019), to our knowledge this is the largest single centre study comprising of HIV-positive patients that presented to an ED setting. Previous studies among HIV-positive patients predominantly explored a handful of variables and were mostly conducted in outpatient settings. This study is unique in that it analysed over 30 variables in HIV-positive patients presenting to an ED with an acute illness presentation.

In addition to describing the profile of presentation of patients enrolled in this study (chapter 2), factors influencing other important aspects relating to the care of acutely ill HIV-positive patients such as ART adherence (chapter 3), length of hospital stay (chapter 4), and in-hospital mortality (chapter 5) were also investigated. Finally, the data was used to develop and internally validate an outcome prediction model (HIV-IMP model) for use in predicting in-hospital mortality in HIV-positive patients presenting with an acute illness (chapter 6).

Profile of presentation of HIV-positive patients

Study findings pertaining to the general description of the collected data are presented in article 1 (chapter 2). The article highlights the high proportion of study patients that had presented with an opportunistic infection or other HIV-related acute illness (greater than two-thirds of study participants). Although these findings are similar to those of a large systematic review (Ford et al., 2015), it is still of concern, considering that ART is freely available in South Africa (Cullinan, 2016).

The relatively low mean CD4 cell count (209 cells/mm^3) in the overall population and the high proportion of study patients with a CD4 cell count <100 cells/mm^3 (47.6%) and a HIV VL >1000 copies/mL (59.0%) is also concerning. In comparison, a systematic review reported a mean CD4

cell count of 257 cells/mm^3 among the 13 studies that were conducted in South Africa, with a significant increase in the CD4 cell count of 39.9 cells/mm^3 per annum (p = 0.02) (Siedner et al., 2014). Since these studies were conducted in the non-ED setting, it is not surprising that the mean CD4 cell count was lower in the current study that predominantly comprised patients presenting with an acute illness.

The current study also found that among participants enrolled in the study, there were high rates of anaemia (haemoglobin < 11 g/dL in 56.3%), leukopenia (white cell count <4.0 x 10^9/L in 15.1%), thrombocytopaenia (platelet count <150 x 10^9/L in 19.9%) renal dysfunction (urea >10 mmol/L in 25.9% and creatinine >120 μmol/L in 29.3%), elevated CRP (CRP >100 mg/L in 48.7%), hyperlactataemia (lactate >2 mmol/L in 42.0%) and hypalbuminaemia (albumin <35 g/L in 60.8%). Previous studies in HIV-positive patients have also reported a high prevalence of anaemia (Chalamilla et al., 2012; Cuong et al., 2012; Gupta et al., 2011; Poka-Mayap et al., 2013), whereas the rates of renal dysfunction ranged between 2.9% and 18% in three earlier studies (Franceschini et al., 2005; Lopes et al., 2011; Wyatt et al., 2006). One particular study found the prevalence of hyperlactatemia to be 8.5% in patients receiving NRTI (Hocqueloux et al., 2003). However, none of these studies were exclusively conducted in HIV-positive patients presenting with an acute illness.

Factors associated with ART non-adherence and reasons for non-adherence

Study findings pertaining to this aspect of the study are presented and described in article 2 (chapter 3). This study is unique in that participants comprised patients that presented to the ED with an acute illness, unlike previous similar studies that were mostly confined to non-acutely ill patients attending out-patient ART clinics. Notable finding of this study were the high proportion of participants that were first diagnosed with HIV at ED presentation (17.2%), the relatively low proportion of participants diagnosed with HIV and initiated on ART >1 month prior to ED presentation (83.3%) and the overall high rate (32.2%) of ART non-adherence among participants. Although some of the study findings were similar or better than previous studies (Hansoti et al., 2018; Ortego et al., 2011), they are nonetheless concerning considering that at the time of data collection, ART was freely available to all South Africans with HIV (Cullinan, 2016). While it is not surprising that the CD4 cell count and HIV VL were significantly lower

among ART non-adherent participants, it is also of concern that younger age and male gender were particularly associated with ART non-adherence. This is in keeping with findings of a large systematic review that included 146 studies from sub-Saharan Africa (Heestermans et al., 2016). The above findings underscore the need to improve on current HIV awareness efforts with particular emphasis on the importance of early testing, fast-tracking of ART initiation while paying particular attention to younger patients and males.

With regard to the reasons for ART non-adherence, the findings of this study were similar to previous studies that have been referenced in the manuscript. Efforts should be concentrated on targeting some of the most prevalent reasons such as 'forgetfulness', 'lack of social support', 'depression/ stress/ mental illness' and 'no transport money to collect medication'. Consideration should be given to implementing practical and cost-effective solutions such as sending out daily text messages, involving family and friends with consent of the patient, psychological support, and direct delivery of medication to the patient.

Prolonged hospital length of stay

As has been described in article 3 (chapter 4), there is a paucity of publications in this domain thereby limiting comparisons to the findings of this study. In addition, compared to the more than 30 parameters that were investigated in this manuscript, previous studies have only focused and reported on a limited number of parameters. The median LOS of 4.6 days recorded in this study, highlights the similarity between two North American studies (USA and Canada) that both reported similar durations (Barbour et al., 2009; Krentz et al., 2006). In contrast, two South American studies (Brazil and Colombia) and a Portuguese study reported a much longer median LOS ranging from 11 to 15 days (Álvarez Barreneche et al., 2017; Coelho et al., 2017; Dias et al., 2009). Although the two North American countries have a higher human development index rating than the countries of the latter three studies, this may not explain the large disparity between regions, as the current study which was conducted in South Africa, shares a similar index to the latter three countries yet has a median LOS similar to the North American studies. A possible reason may be related to the high burden of HIV and resource utilisation in South Africa (Long et al., 2012), which may have resulted in earlier discharge to free up bed capacity.

The discussion section of this article also highlighted the paucity of data pertaining specifically to LOS. In fact, upon review of the literature only four previous studies were identified to compare to the findings of this study. These four studies identified several factors, including the number of comorbid conditions and inpatient procedures, the presence of tuberculosis, a low CD4 cell count, an AIDS defining illness, as well as no current use of ART and low income that were associated with prolonged hospitalization. In contrast they also found that other factors such as female sex, emergent admission, in-hospital mortality, pneumocystis jirovecii pneumonia, and hepatitis C virus co-infection were associated with a shorter LOS (Augusto et al., 2019; Gonçalves and Ferreira, 2013; Krentz et al., 2006; Santella et al., 2010). Comparatively, after multivariate analysis of the current study data, haemoglobin <11 g/dL, GCS <15, creatinine >120 μmol/L and cryptococcal and bacterial meningitis were associated with a longer LOS, while bacterial pneumonia and acute gastroenteritis were associated with a shorter LOS.

Predictors of in-hospital mortality

These findings were presented and described in article 4 (chapter 5). Although many of the variables identified may also be predictors of mortality and severity of illness in patients with other non-HIV related illnesses (Capuzzo et al., 2000), the combination of variables identified in this study is unique. To our knowledge, this is the largest and most comprehensive single-centre study to have determined predictors of mortality in consecutive HIV-positive patients presenting to an ED setting. Overall, 29 variables were significantly associated with in-hospital mortality on univariate analysis while nine (ART non-adherence or ART naive, GCS <15, respiratory rate >20 breaths/min, oxygen saturation <90%, white cell count <4.0 x 10^9/L, creatinine >120 μmol/L, lactate >2 mmol/L, albumin <35 g/L and cryptococcal meningitis were associated with in-hospital mortality after subjecting the data to multivariate analysis.

Age (Biset Ayalew, 2017; Dias et al., 2009; Rubaihayo et al., 2015), male sex (Angdembe et al., 2019; Dias et al., 2009; Rubaihayo et al., 2015), unemployment (Biset Ayalew, 2017), having no schooling or only primary school education (Biset Ayalew, 2017), multiple diagnoses (Dias et al., 2009), poor treatment adherence (Biset Ayalew, 2017), low CD4 cell count (Angdembe et al., 2019; Biset Ayalew, 2017; Rubaihayo et al., 2015), anaemia (Biset Ayalew, 2017;

Johannessen et al., 2008; Russell et al., 2010; Sullivan et al., 1998), thrombocytopaenia (Johannessen et al., 2008), lymphopenia (Johannessen et al., 2008), raised CRP (Drain et al., 2007; Feldman et al., 2003; Lau, 2006), hypalbuminaemia (Feldman et al., 2000; Lang et al., 2013; Sudfeld et al., 2013), tuberculosis (Biset Ayalew, 2017), bacterial meningitis and cryptococcal meningitis (Jarvis et al., 2014; Wall et al., 2013) were reported to be predictors of mortality in previous studies.

The HIV in-hospital mortality (HIV-IMP) risk score

This has been presented and described in article 5 (chapter 6). The HIV-IMP risk score is the first outcome prediction risk score to have been developed and internally validated for use in HIV-positive patients requiring hospital admission. Eight of the nine variables that were identified in article 4 as independent predictors of in-hospital mortality were included in the score. Although cryptococcal meningitis was also an independent predictor of in-hospital mortality, it was omitted from the risk score as the diagnosis is not as readily available as the other eight included predictors, which are relatively easily obtained or measured as they mostly comprise vital signs and basic laboratory findings that are rapidly available in facilities that have access to in-unit point-of-care (POC) testing. It is a score that can be easily and fairly rapidly calculated.

An additional advantage is that the risk score was also internally validated using the bootstrap method, which has been shown to be superior to other methods (Steyerberg et al., 2001). Using this method, the risk score retained good discrimination and calibration as depicted by the AUROC and the Hosmer-Lemeshow goodness of fit test, respectively.

Similar to currently existing mortality prediction models such as the APACHE II (Knaus et al., 1985), SOFA (Vincent et al., 1996) and qSOFA (Seymour et al., 2016) scores that were developed for use in acutely ill hospitalised patients in general, the HIV-IMP risk score has been developed for use in HIV-positive patients presenting to the ED with an acute illness with the aim of predicting in-hospital mortality. The APACHE II score has been shown to overestimate mortality approximately two-fold in HIV-positive patients in the ICU (Maphula et al., 2020), indicating that the presentation and prognosis of HIV-positive patients may be different from that

of other diseases, hence the need to develop a score specific to HIV-positive patients presenting with an acute illness.

8.2 Study limitations

This was a single centre study and data was collected over a relatively short duration of 15 months. Our overall findings may not fully reflect the actual dynamics of the HIV-positive population residing within the drainage area of the hospital since the study site is designated as a tertiary level academic hospital and as such patients with less severe presenting illnesses are triaged out to a lower-level of care facility. Besides differences in triage criteria between facilities, other factors such as admission and discharge criteria, resource availability, clinical management protocols and clinician skill may also differ between facilities.

An additional limitation is that chronic comorbid conditions such as hypertension, diabetes and coronary vascular disease were not taken into account and outcomes after hospital discharge were not determined as patients were not followed-up after discharge. Also, some of the presenting diagnoses, such as community acquired pneumonia, were based on clinical suspicion and may not have been objectively confirmed (e.g., laboratory culture), hence, it is possible that some of the presenting diagnoses may have been over- or underestimated. Furthermore, differences between participants that were on ART and those that were not, or were ART non-adherent, were not taken into account when interpreting the median CD4 cell count and HIV VL in chapters 4 and 5 that determined the predictors of hospital LOS and in-hospital mortality, respectively. Since the ACTG-AQ questionnaire was utilized to determine ART non-adherence, this may have resulted in under-reporting of overall adherence, as the questionnaire only accounts for non-adherence within the past two weeks of patient presentation. Further, as the reasons for a low CD4 cell count and high VL were not explored, it is likely that the relatively high proportion of ART adherent participants with a high VL and low CD4 cell count may also indicate that ART non-adherence rates were possibly higher than reported. In addition, some of the reasons for ART non-adherence, such as forgetfulness, could have been explored further.

With regard to hospital LOS, it is possible that some patients may have been readmitted for the same illness shortly after having been discharged, which was not considered when calculating

the LOS. In addition, the study did not account for patients that were discharged for continuation of care to a rehabilitation or step-down facility.

There are also specific limitations that pertain to the chapters on the predictors of in-hospital mortality and the development and internal validation of the HIV-IMP risk score. Firstly, since patients were not followed up after discharge, mortality shortly after discharge was not reported. It is likely that some terminally ill patients were discharged for palliative care and may have demised shortly after discharge. Overall, there is a need to externally validate the model prior to clinical use.

8.3 Study conclusions

Despite more than thirty years of the African HIV pandemic, PLWH are still at risk of serious morbidity and inappropriate mortality. With regard to ART, HIV-positive patients presenting to the ED that were not on ART, had significantly higher in-hospital mortality compared to those on ART. Factors that were significantly associated with ART non-adherence included younger age, male sex, CD4 cell count <100 cell/mm^3, HIV VL >1000 copies/mL, lack of viral suppression (HIV VL <50 copies/mL), a higher NEWS-2 score, and length of hospital stay >5 days.

A haemoglobin <11 g/dL, GCS <15, creatinine >120 μmol/L, cryptococcal meningitis and bacterial meningitis were predictive of a longer hospital LOS whereas bacterial pneumonia and acute gastroenteritis were predictive of a shorter hospital LOS among HIV-positive patients presenting to the ED. With regard to in-hospital mortality, routine clinical and laboratory parameters such as respiratory rate >20 breaths/min, creatinine >120 μmol/, oxygen saturation <90%, white cell count <4.0 x 10^9/L, ART non-adherence or not yet on ART, GCS <15, albumin <35 g/L, lactate >2 mmol/L and cryptococcal meningitis were independent predictors of in-hospital mortality among HIV-positive patients presenting to the ED. These findings facilitated the development and internal validation of the HIV-IMP risk score for predicting in-hospital mortality in HIV-positive patients requiring hospital admission. The risk score is comprised of only eight predictor variables, is relatively simple to use and exhibits overall good discrimination

and calibration. Future studies should be aimed at externally validating the risk score in varying clinical settings.

For South Africa to achieve their target of ending HIV by 2030, it would require an urgent public health response as well as implementation of innovative strategies to further improve HIV awareness and to improve the quality and accessibility to ART services. The findings of this study may also provide valuable insights in guiding clinical decision making, directing the appropriate use of resources, influencing patient disposition, and facilitating the design of strategies to optimise outcomes in HIV-positive patients presenting to the ED.

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APPENDIX 1: ETHICS CLEARANCE CERTIFICATE

R14/49 Dr Abdullah Laher

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M160512

NAME: (Principal Investigator)	Dr Abdullah Laher
DEPARTMENT:	Emergency Medicine Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Study of HIV Presentations to an Adult Emergency Department and Development and Validation of an Outcome Prediction Model
DATE CONSIDERED:	27/05/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof G Richards, Prof F Paruk and Prof F Venter
APPROVED BY:	Professor P. Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/07/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit to the Committee. I **agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially review in May and will therefore be due in the month of May each year.

Principal Investigator Signature

Date 04/07/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 2: DECLARATION OF STUDENT'S CONTRIBUTION TO ARTICLES AND AGREEMENT OF SUPERVISORS AND CO-AUTHORS

I, Abdullah Laher, student number 9902884f, declare that this Thesis is my own work and that I contributed adequately toward research findings in the published/ submitted articles stated below which are included in my Thesis.

Signature of student:  **Date:** 02 November 2021

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the articles by the student as part of his thesis.

Name	Co-author	Signature	Date
Guy A Richards	Articles 1-5		02 November 2021
Fathima Paruk	Articles 1-5		02 November 2021
Willem DF Venter	Articles 1-5		02 November 2021
Oluwatosin Ayeni	Articles 4-5		02 November 2021
Feroza Motara	Article 5		02 November 2021
Muhammed Moolla	Article 5		02 November 2021

Article 1: Profile of presentation of HIV-positive patients to an emergency department in Johannesburg, South Africa. Southern African Journal of HIV Medicine, 22(1), 1177. https://doi.org/10.4102/sajhivmed.v22i1.1177

Article 2: Antiretroviral therapy non-adherence among HIV-positive patients presenting to an emergency department in Johannesburg, South Africa: Associations and reasons. South African Medical Journal, 111(8), 753-758. https://doi.org/10.7196/SAMJ.2021.v111i8.15604

Article 3: Predictors of prolonged hospital stay in HIV-positive patients presenting to the emergency department. PLOS ONE, 16(4), e0249706. https://doi.org/10.1371/journal.pone.0249706

Article 4: Predictors of in-hospital mortality among HIV-positive patients presenting with an acute illness to the emergency department. HIV Medicine, 22(7), 557-566. https://doi.org/10.1111/hiv.13097

Article 5: Development and internal validation of the HIV In-hospital Mortality Prediction (HIV-IMP) risk score. HIV Medicine, 23(1), 80-89. https://doi.org/10.1111/hiv.13159

APPENDIX 3: PLAIGIRISM DECLARATION AND TURNITIN REPORT

Declaration by Student

I, **Abdullah E Laher** (Student number: **9902884F**), am a student that have been registered for the degree **Doctor of Philosophy** from the year **2016**. I hereby declare the following:

I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
I confirm that ALL the work submitted for assessment for the above course is my own unaided work except where I have explicitly indicated otherwise.
I have followed the required conventions in referencing the thoughts and ideas of others.
I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this i**s** not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.



Prof AE Laher Signature: Date: 02/11/2021

The study supervisors hereby acknowledge their satisfaction with the Turnitin report attached below:



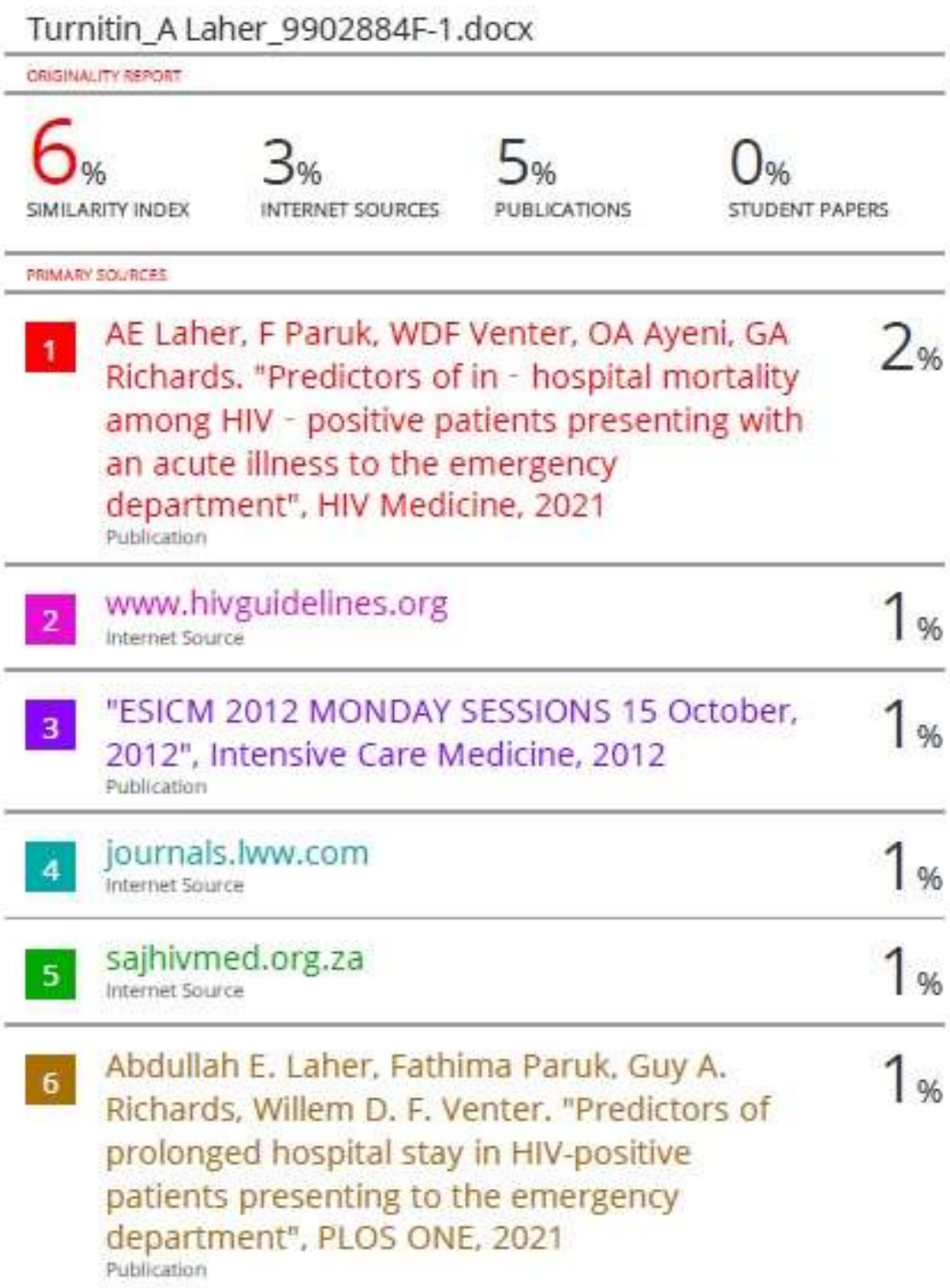
Prof GA Richards Signature: Date: 02/11/2021



Prof F Paruk Signature: Date: 02/11/2021



Prof WDF Venter Signature: Date: 02/11/2021



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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	AE Laher, F Paruk, WDF Venter, OA Ayeni, GA Richards. "Predictors of in - hospital mortality among HIV - positive patients presenting with an acute illness to the emergency department", HIV Medicine, 2021 Publication	2%
2	www.hivguidelines.org Internet Source	1%
3	"ESICM 2012 MONDAY SESSIONS 15 October, 2012", Intensive Care Medicine, 2012 Publication	1%
4	journals.lww.com Internet Source	1%
5	sajhivmed.org.za Internet Source	1%
6	Abdullah E. Laher, Fathima Paruk, Guy A. Richards, Willem D. F. Venter. "Predictors of prolonged hospital stay in HIV-positive patients presenting to the emergency department", PLOS ONE, 2021 Publication	1%

Note: The five published articles that emanated from this research were excluded prior to generating the Turnitin plagiarism report