Reasons Cited for the Interruption of Anti-Retroviral Treatment in the Bloemfontein/Mangaung Area

by

Dr Thomas Ross du Plessis

Submitted in fulfilment of the requirements for the degree

MASTER OF MEDICINE IN FAMILY MEDICINE

in the

DEPARTMENT OF FAMILY MEDICINE
FACULTY OF HEALTH SCIENCES

at the

UNIVERSITY OF THE FREE STATE.

Supervisor: Dr M van Lill

Biostatician: Me. R. Nel

30 November 2020

Declaration of Authorship

I, Thomas Ross du Plessis, declare that the coursework Master's Degree mini-dissertation that I herewith submit in a publishable manuscript format for the Master's Degree qualification MMed Family Medicine at the University of the Free State is my independent work, and that I have not previously submitted for a qualification at another institution of higher education.

16/04/2021

Signature | Date

Dr Thomas Ross du Plessis – Researcher

Signature

Dr Maresa van Lill - Supervisor

Acknowledgements

- Dr M van Lill, my supervisor during this research project.
- Me R Nel, for the statistical analysis and advice with regards to interpretation, as well as the initial structure of the data sheet.
- Prof WJ Steinberg, for his insight, support, and contributions.
- Sr M Magau, for conducting the interviews and collecting the data
- Mr J Botes for assistance with the formatting.
- Thank you to the Department of Family Medicine for the valuable inputs during the protocol approval process and allowing dedicated research time to work on this research project.

Table of contents

Abstract

Background:

HIV infection is a chronic condition that affects millions of people worldwide and causes significant morbidity and mortality. It is however treatable with anti-retroviral treatment. This does require regular, uninterrupted dosages to prevent the development of treatment resistance. There are many reasons why patients may be unable to remain compliant on their treatment including medication, healthcare and psycho-social reasons.

Objectives:

To investigate the reasons cited for treatment interruption of anti-retroviral treatment in patients admitted to National District Hospital from the Mangaung district.

Methods:

This was a prospective descriptive study. Data was obtained by voluntary structured interviews from patients admitted to National district hospital between February and April of 2020. A total of 17 patients were included.

Results:

Unemployment among participants was at 68%, with 54% reporting no consistent income.

There was a fairly even spread of reasons cited for treatment interruption between the healthcare, medication and psychosocial factors. Stock issues, however, remained a prominent problem reported. Almost half of participants reported omissions in their counselling prior to treatment initiation. Medication side effects remains a problem with 52% of participants reporting side effects and 44% of those attributed non-compliance to it.

The majority of patients reported good family support and fear of disclosure or stigma was not reported.

All participants screened positive for symptoms of depression, with 52% falling into the moderate and severe depression categories.

Conclusions:

The challenges for people living with HIV to remain compliant with their treatment remains numerous and varied. The role that unemployment and poverty plays cannot be ignored. Continuing efforts need to be made to create a robust supply of medication to patients if good outcomes are to be achieved. Patients need to be well educated prior to treatment initiation and given good advice regarding the management of side effects.

The prevalence of symptoms for Depressive Mood disorder in this patient population is high and needs to be actively screened for at initiation and follow-up of patients.

Further research within more well-defined communities can be beneficial for the healthcare workers working in those areas.

Keywords

- HIV
- Anti-retroviral treatment
- Adherence
- Compliance
- Treatment interruption
- South Africa
- Reasons

List of abbreviations

AIDS	–	Acquired immune deficiency syndrome
ART	–	Anti-retroviral treatment
DNA	–	Deoxyribonucleic acid
CD4	–	Cluster of differentiation 4
COVID-19	–	Coronavirus disease 2019
FS DoH	–	Free State Department of health
GCS	–	Glasgow coma scale
HCW	–	Health care worker
HSREC	–	Health sciences research ethics committee
HIV	–	Human immunodeficiency virus
MMED	–	Masters of medicine
NDH	–	National district hospital
PHQ-9	–	Patient health questionnaire 9
SA	–	South Africa
TB	–	Tuberculosis
UFS	–	University of the Free State
UNAIDS	–	United nations program for acquired immune deficiency syndrome

List of appendices

Chapter 1: Literature Review

The human immune system is comprised of different mechanisms. These include physical barriers such as skin, cellular mechanisms and anti-body responses. The CD4 cells are a subclass of T-helper cells that are integral to immunological communication and antigen presentation. They thus help regulate the immune system and it's responses to infections.

The human immunodeficiency virus (HIV) is a retrovirus that targets human CD4 lymphocytes at its site of replication[1]. Via reverse transcriptase enzymes the virus incorporates its genes into the deoxyribonucleic acid (DNA) of the lymphocyte thereby causing it to continually produce copies of the virus and its associated proteins. This process is prone to errors and thus produces numerous genetically heterogenic versions of the virus due to the resultant mutations. This means that the virus has the potential for rapid development of resistance when the viral replication is not suppressed. The infection causes a progressive immune deficiency by among other mechanisms the destruction of CD4 cells as well as the demodulation of the immune system[1]. It is also associated with numerous other complications including renal disease, vasculitis, venous thrombosis and thromboembolism, cerebrovascular accident, cancers and auto immune conditions[1]. It is predominantly spread through sexual transmission, but can be transmitted through needle sharing or through other body fluids such as blood coming in contact with broken mucous membranes or skin.

HIV infection is a major cause of concern worldwide, with approximately 36 million people living with the condition worldwide, but even more so in sub-Saharan Africa and specifically in South Africa (SA). According to statistics SA, approximately 12.6% or 7.1 million of South Africa's population is living with HIV[2]. In the 15-59 years of age group the prevalence is even higher at 18%. The infection rate among women is higher still, with many pregnant women being infected. Fifty six percent of the population living with HIV are on anti-retroviral treatment (ART) as of 2016, with a 95% treatment rate for pregnant females[3]. According to United Nations program for AIDS (UNAIDS), 110 000 deaths in 2016 in South Africa could be attributed to HIV[2].

On a socio-economic level the pandemic has many effects. The number of people who are dependent on government or social support increases as people become too ill to take care of themselves and their families. Orphans increasingly end up as the heads of families attempting

to make ends meet. The highest prevalence occurs in the working age group(15-59 years of age)[2,3]. Consequently, there is a direct impact on the work force and productivity. This means loss of gross domestic production and tax revenue for the country as well as the damages to the individual businesses with work days lost due to frequent illness or the loss of workers due to HIV related deaths[4]. The South African government has budgeted R205Bn for the department of health, with R66.4Bn allocated to the treatment and prevention of HIV[5]. This does not account for the further increase cost in hospitalization and treatment of infection and other health impacts of HIV (for example cerebrovascular accidents, lymphoma, Kaposi sarcoma etc.) There are approximately 1.3 million acquired immunodeficiency syndrome (AIDS) orphans in South Africa as of 2016 placing a severe strain on the social services of the country[2].

The burden of HIV and AIDS has been significantly decreased with the use of effective ART as well as progressively more inclusive guidelines for ART initiation. This has increased life expectancy and decreased morbidity leading to generally longer lives with fewer complications[3,6]. New HIV infections peaked in 1998. An estimated 560 000 people being infected with the condition in that year compared to an estimated 270 000 in 2016. The number of people living with the condition is still increasing though as the infection rate is still considerably higher than the death rate which has been steadily improving thanks to the measures that have been implemented. The peak of annual deaths was in 2006 with an estimated 280 000 people dying because of the disease[2].

On a psychosocial level HIV infection is associated with deteriorating functional status due to opportunistic infections and HIV wasting syndrome. It also carries with it significant emotional problems as patients experience the stigma associated with the illness as well as the depression and anxiety that so called “dread diseases” carry with them. Interpersonal relationships can be significantly complicated due to the condition, especially in cases of discordant couples[7]. HIV infected people were found to be poorer than those living without HIV and were generally ill more of the time[8]. These factors have been shown to have a significant impact on patient adherence to ART. Patient personality has been shown to affect adherence and it has been shown that treating depression has a significant effect on improving adherence to ART[9,10].

Good compliance to ART has been shown to improve patient outcomes[6]: with sufficient adherence to highly active anti-retroviral treatment, viral replication in CD4 cells can be suppressed. This leads to decreased viral loads and improved CD4 counts. As the immune

system functionality improves, the incidence of opportunistic infections decreases leading to improved quality of life and general function. Especially important in the South African setting is the improved resilience to tuberculosis (TB) infection, a leading cause of death and morbidity in this disease population.

Poor adherence to ART is associated with diminishing immune system function and opportunistic infections as well as HIV treatment resistance[1,11]. This leads to increased viral loads in patients which in turn increases the likelihood of transmission of the infection both in mother to child transmission and to sexual partners[12]. With unsuppressed viral loads the patient's CD4 count and immune function will progressively decline as the virus replicates.

The importance of ensuring proper adherence to ART is thus obvious, but how can we assist patients in taking their medication consistently? To answer this question, factors influencing adherence need to be identified. This is clearly a multifactorial problem that likely will have causes that will be specific to the community that is being serviced as well as broader themes that can be found in other studies. Previous studies looking at the barriers to adherence uncovered larger themes or categories of problems that can be explored. These are typically classified as:

1. Patient related
2. Socio-economic
3. Medication
4. Health care team and system

This classification made it easier to assess the different problems. Issues that have previously been identified under these headings include:

Patient related:

Experiencing better health[13]

Some patients reported that once their health had improved, they tended to forget to take their treatment as their symptoms that reminded them that they are sick were no longer there. Others no longer saw the need to take their medication since they feel better, or would plan to take the medication only if they felt ill again.

Forgetfulness[13]

Unintentional missing of doses due to their mind being occupied by other concerns is a prominent feature in certain settings. Occasionally forgetting drug doses is understandable, but also something that can be avoided with appropriate strategies around reminders that can be implemented and could be taught universally during the counselling before treatment. This forgetfulness can be further exacerbated by the following point as well.

Pessimism/depression[9,10,13]

Depression can have numerous effects that can impact compliance to treatment. It can affect memory, motivation, and drive. Some patients actually stop their treatment with the reported intent as a means to end their lives. A meta-analysis of 95 studies, conducted in 2011, found a significant correlation between depression and non-adherence to treatment. This was in line with results with regards to the effect of depression on treatment adherence for other chronic conditions. There was also evidence for the beneficial effect of implementing treatment for depression, such as cognitive behavioural therapy, on treatment compliance.

Emotional distress[13]

During emotional crisis patients reported that they would often neglect to take their treatment. This is often the case during interpersonal conflict, especially in the home setting. Episodes of life stress have been shown to have a direct detrimental impact on treatment adherence, regardless of coping strategies used by the individual. This limits the value that cognitive strategies can play, but also highlights the importance of HCWs asking about current life events of patients and the need for good social support and reminder strategies for maintaining adherence.

Alcohol or drug use[13-16]

Substance abuse can have a negative effect on the consistency of medication use. This can happen as a direct effect of intoxication, with subsequent forgetting of doses, or because of the preoccupation with obtaining the substance itself. It can also have socioeconomic implications that can compound other factors that can negatively impact adherence. Often drug dependence can lead to eroding social support structures, loss of employment, and declining health status.

Religious or cultural[13,15,16]

Some patients reported that they would rather use traditional medicine or that their faith would cure them. In certain settings reliance on medication may be considered as a sign of weak faith and there could be considerable internal and community pressure to rely on divine healing. The variation in religious and cultural worldview can be difficult to understand, respect and manage, especially in the context of diversity often encountered in urban areas. Furthermore, the nature of religious belief means that simple reasoning without deep understanding of the patient's views, will be ineffective and might undermine the healthcare worker (HCW)-patient relationship.

Socio-economic:

Lack of money for food[13,17]

Not having food to eat places a mental and physical burden on people, it is after all one of our most basic needs. Hunger leads to a focussed drive to obtain food, often at the expense of other considerations such as taking one's medication. Eating prior to taking ART is also a common strategy to mitigate gastrointestinal side effects that can be experienced.

Unable to afford transport[13,18]

Being able to access healthcare is an obvious prerequisite to continually obtaining prescribed medication. As such the distance to the clinics, cost involved, and availability of transport can all have a significant impact on compliance. This factor is often overlooked in settings where the healthcare is provided free of charge and there may be insufficient consideration given to the costs surrounding a clinic visit. This is also a highly variable factor as even for some in very low-income settings the clinic may be within walking distance whereas other may face difficulty accessing transport even if they have the means to pay for it.

Disability grants[13]

In cases where patients were incapacitated by late stage AIDS, they would be eligible for temporary grants from the government. Some of these patients would stop taking treatment in the hope of obtaining or perpetuating a grant. Whether or not the prospects of obtaining this is realistic or not, the possibility of obtaining short term income when faced with severe poverty may often trump long term health.

Stigma[13]

Certain communities still face significant stigma associated with HIV infection and this social aspect may discourage people from continuation of care. The fear of victimisation or being ostracized can be a potent driver of behaviour. Both internalised and external stigma can be instrumental in the delay or avoidance of health seeking behaviour[22]. The individual's preconceived notions about the condition may play into the stigma they expect others to place upon them should their status be revealed and can thus play an important role in the way the person interprets interactions with others and may fuel denial and avoidance of dealing with their condition or disclosing their status.

Fear of disclosure[13,19]

Related to the stigma associated with the condition, many people fear that by attending clinics (especially dedicated HIV clinics) their diagnosis will be made obvious to the community. This concern is made all the more realistic within the primary healthcare setting with clinic service areas geographically dictated meaning that one is more likely to encounter one's neighbours within the setting of a community healthcare centre or clinic.

Medication related

Side effects[13,16]

Patients reported that they would stop treatment as they could not cope with the side effects. The side effects of ART are well documented and can have detrimental effects on daily function. When adverse effects impact on the ability of individuals to work there can be an understandable conflict between long term healthcare compliance and the effects that can have on their career and income in the short term. This is even more pertinent in the context of informal labour where there is no protected income.

Adverse effects such as nausea, vomiting, and perceptual disturbances' effect on quality of life should not be underestimated. The individual's knowledge of the importance of consistent treatment use and their drive to comply with it is clearly very important to help facilitate compliance in the face of unpleasant side effects. It is however also important that the patients are empowered to report the side effects that they experience to their HCWs so that coping strategies may be implemented or that the regimen may be changed.

Pill burden[20]

This was a prominent factor in patients who had to take ART as well as treatment for other conditions such as TB. As the number of medications that need to be taken daily increases the complexity of the regimen grows and can become confusing. Different dosage intervals can compound the confusion. This is all made more difficult when one considers the low level of literacy that some patients have.

Having to take large numbers of pills can be disheartening, but it also increases the likelihood of drug interactions and side effects. When multiple treatments are started simultaneously, as often is with the diagnosis of late stage HIV, it may be difficult to identify the offending drug or the patient may default the treatment as a whole.

Health care team and system

Poor patient education[13,15]

Patient education is central to good clinical practice, but it is especially important in the context of chronic or life-long treatments. In the case of ART, it is essential for the patients to understand the chronic nature of their condition and its treatment. If a patient knows why it is important to take the medication regularly (not just when they feel ill for example) can help motivate patient cooperation in their treatment. Warning them of potential side effects and ways of mitigating or avoiding them can be instrumental in ensuring compliance.

Follow up scheduling[13]

The administrative systems need to ensure that patient follow ups are scheduled in such a way that prescriptions remain valid before next follow up, visits are scheduled as such that their medication supply is not exhausted prior to date for treatment collection, and that it is feasible for the patient to attend. Rigid clinic scheduling systems are often easier to administrate, but may fail to serve the patient's needs. It is important that some flexibility be available within the system to ensure that patients are able to actually attend clinic regularly.

Breakdown of patient-carer relationship[15]

The relationship between the healthcare worker and the patient is a foundational part of healthcare. For effective communication and treatment compliance to take place the patient needs to trust the healthcare worker, and the healthcare worker needs to be able and willing to listen to the patient's concerns and problems. If this relationship breaks down compliance can

be adversely affected. Problems with regards to side effects, optimal dosing times and social issues, for example, may go un-raised due to the deteriorating relationship. This again compounds those barriers to adherence instead of the HCW being a resource to help manage problems like these. When trust in the HCW or healthcare system as a whole is eroded more credence may be given to alternative narratives that may compromise compliance further.

Long Waiting times and overcrowding[15,16]

Many patients cited long periods as contributing to poor compliance. Waiting times can affect compliance in multiple ways. On a basic human level, we are impatient and can become demotivated by having to wait long periods of time. It can adversely affect work responsibilities by having to take full days, sometimes even more than one, off work on a monthly basis. This leads to loss of productivity as well as places a strain on employer-employee relationships.

Working hours of facilities[15]

The working hours of the healthcare facilities can play a large role in whether patients are able to negotiate their social and work responsibilities to be able to attend their clinic. Inflexibility with regards to the scheduling of appointments to suit the patients as well as working within the system can be implicated as a challenge for patients to attend clinic regularly.

It is clear how much variety there is to the reasons why each individual patient may interrupt their ART, thus it becomes very important to understand the main factors prevalent in the communities one serves especially from the point of view of family medicine and community oriented primary care. Only once a proper understanding of the problems has been gained can one develop plans to address them.

Developing strategies to maximise the consistent use of ART should be a priority due to the multiple knock-on effects one can expect. With improved compliance comes improved immunity and health. This resilience helps in the fight against tuberculosis and infectious conditions in general, saving lives and health care costs and resources. The improved functional state of patients can lead to increased productivity, psychosocial conditions and healthier communities. Once the key drivers of non-adherence are identified, the community should be involved in developing ways to address the problems. With community investment and commitment, many opportunities can arise to support people living with HIV. Without community involvement efforts will remain slow and difficult. This approach is in line with

the “Batho Pele Principles” that are espoused by the government in its service delivery. These principles should be acknowledged and integrated in the way we as healthcare workers strive to serve our communities.

It is hoped that this research will help to elucidate the reasons why patients in our community are unable to remain compliant so that the dialogue can be started around possible solutions. Hopefully it will also help inform HCWs about the challenges faced by our patients and foster greater empathy.

References:

1. Davidson SS. Davidson' s Medicine. Davidson's principles and practice of medicine. 2010. 384–408 p.
2. UNAIDS. Fact sheet - Latest global and regional statistics on the status of the AIDS epidemic. UNAIDS Fact Sheet 2017. 2017.
3. Statistics SA. Mid year population estimates. Vol. 8. 2018.
4. Ellis LL, Smit BW, Laubscher P. The Macro-economic Impact of HIV/AIDS in South Africa. J Stud Econ Econom. 2003;27(2):1–28.
5. National Treasury of South Africa. Budget Review 2018. 2018.
6. Bor J, Herbst AJ, Newell ML, Bärnighausen T. Increases in adult life expectancy in rural South Africa: Valuing the scale-up of HIV treatment. Science (80-). 2013;
7. Romel D. Mackelprang, Rose Bosire Brandon L. Guthrie, Robert Y. Choi, Amy Liu, Anne Gatuguta, Anne F. Rositch, James N. Kiarie CF. High rates of relationship dissolution among HIV-serodiscordant couples in Kenya. AIDS Behav. 2014;18(1):189–93.
8. Bachmann MO, Booysen FLR. Health and economic impact of HIV/AIDS on South African households: A cohort study. BMC Public Health. 2003;3:1–8.
9. Moosa MYH, Jeenah FY. Treating depression in HIV-positive patients affects adherence. South Afr J HIV Med. 2017;13(3):144–9.
10. O'Cleirigh C, Ironson G, Weiss A, Costa PT. Conscientiousness Predicts Disease Progression (CD4 Number and Viral Load) in People Living With HIV. Heal Psychol. 2007;26(4):473–80.
11. Gardner EM, Sharma S, Peng G, Hullsiek KH, Burman WJ, MacArthur RD, et al. Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance. AIDS. 2008;
12. Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: Systematic review and meta-analysis. Aids. 2009;23(11):1397–404.
13. Azia IN, Mukumbang FC, Van Wyk B. Barriers to adherence to antiretroviral

treatment in a regional hospital in Vredenburg, Western Cape, South Africa. South Afr J HIV Med. 2016;

14. Begley K, McLaws ML, Ross MW, Gold J. Cognitive and behavioural correlates of non-adherence to HIV anti-retroviral therapy: Theoretical and practical insight for clinical psychology and health psychology. Clin Psychol. 2008;12(1):9–17.

15. Kip E, Ehlers VJ, Van Der Wal DM. Patients adherence to anti-retroviral therapy in Botswana. J Nurs Scholarsh. 2009;41(2):149–57.

16. Dahab M, Charalambous S, Hamilton R, Fielding K, Kielmann K, Churchyard GJ, et al. "That is why I stopped the ART": Patients' & providers' perspectives on barriers to and enablers of HIV treatment adherence in a South African workplace programme. BMC Public Health. 2008;8:1–6.

17. Weiser SD, Tuller DM, Frongillo EA, Senkungu J, Mukiibi N, Bangsberg DR. Food insecurity as a barrier to sustained antiretroviral therapy adherence in Uganda. PLoS One. 2010;5(4).

18. J.S. M, L. I, F. L, P. F, H. B. Antiretroviral therapy in resource-poor settings: Decreasing barriers to access and promoting adherence. J Acquir Immune Defic Syndr [Internet]. 2006;43(SUPPL. 1):S123–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2006602950

19. Rodger AJ, Lascar M, Collins S, Perry N, Daskalopoulou M, Wilkins E, et al. Non-Disclosure of HIV Status and Associations with Psychological Factors, ART Non-Adherence, and Viral Load Non-Suppression Among People Living with HIV in the UK. AIDS Behav. 2016;21(1):184–95.

20. Ruanjahn G, Roberts D, Monterosso L. An exploration of factors influencing adherence to highly active anti-retroviral therapy (HAART) among people living with HIV/AIDS in Northern Thailand. AIDS Care - Psychol Socio-Medical Asp AIDS/HIV. 2010;22(12):1555–61.

21. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med. 2001;

22. Simbayi, L. C., Kalichman, S., Strebel, A., Cloete, A., Henda, N., & Mqeketo, A. (2007). Internalized stigma, discrimination, and depression among men and women living with HIV/AIDS in Cape Town, South Africa. Social Science and Medicine. https://doi.org/10.1016/j.socscimed.2007.01.006

Chapter 2: Publishable Manuscript

The publishable manuscript was prepared with the guidelines for intended journal of South African Medical Journal.

Journal:	South African Medical Journal
URL:	http://samj.org.za/index.php/samj
Title:	Reasons Cited for the Interruption of Anti-Retroviral Treatment in the Bloemfontein/Mangaung Area
Number of words:	4210

Type of manuscript: Original Research

Title:

Reasons Cited for the Interruption of Anti-Retroviral Treatment in the Bloemfontein/Mangaung Area

Authors:

TR du Plessis
MBChB, Family Medicine Registrar
Department of Family Medicine, University of the Free State
ross.duples@gmail.com

M van Lill
MBChB, MMed (Fam)
Department of Family Medicine, University of the Free State
m.vanlill.m@gmail.com

M Nel
M.Med.Sc. Biostatistics
Department of Biostatistics, University of the Free State
gnbsmn@ufs.ac.za

Corresponding author:
TR du Plessis
e-mail: ross.duples@gmail.com
Tel: +27 72 495 9164
Department of Family Medicine G19
PO Box 339
University of the Free State
Bloemfontein 9301

Abstract

Background: HIV infection is a chronic condition that affects millions of people worldwide and causes significant morbidity and mortality. It is however treatable with anti-retroviral treatment. This does however require regular, uninterrupted dosages to prevent the development of treatment resistance. There are many reasons why patients may be unable to remain compliant on their treatment including medication, healthcare and psycho-social reasons.

Objectives: To investigate the reasons cited for treatment interruption of anti-retroviral treatment in patients admitted to National District Hospital from the Mangaung district.

Methods: This was a prospective descriptive study. Data was obtained by voluntary structured interviews from patients admitted to National district hospital between February and April of 2020. A total of 17 patients were included.

Results: Unemployment among participants was at 68%, with 54% reporting no consistent income.

There was a fairly even spread of reasons cited for treatment interruption between the healthcare, medication and psychosocial factors. Stock issues, however, remained a prominent problem reported. Almost half of participants reported omissions in their counselling prior to treatment initiation. Medication side effects remains a problem with 52% of participants reporting side effects and 44% of those attributed non-compliance to it.
The majority of patients reported good family support and fear of disclosure or stigma was not reported.
All participants screened positive for symptoms of depression, with 52% falling into the moderate and severe depression categories.

Conclusions: The challenges for people living with HIV to remain compliant with their treatment remains numerous and varied. The role that unemployment and poverty plays cannot be ignored. Continuing efforts need to be made to create a robust supply of medication to patients if good outcomes are to be achieved. Patients need to be well educated prior to treatment initiation and given good advice regarding the management of side effects.

The prevalence of symptoms of depression in this patient population is high and needs to be actively screened for.

Further research within more well-defined communities can be beneficial for the healthcare workers working in those areas.

Keywords:

HIV; Anti-retroviral treatment; Adherence; Compliance; Treatment interruption; Reasons

Introduction

The human immunodeficiency virus (HIV) is a retrovirus that targets CD4 leukocytes as its site of replication. It incorporates itself into the DNA of the leukocytes via its reverse transcriptase enzyme, thus causing the cells to continually produce more copies of the virus and its proteins[1]. Symptoms from HIV infection comes mostly from opportunistic infections due to the decreased function of the immune system, but numerous other complications can also occur[1]. These include renal disease, thrombo-embolic conditions, and increased incidences of cancers and auto-immune conditions[1]. The infection is spread through sexual contact as well as other ways where bodily fluids can come in contact with damaged mucosa or skin[1].

HIV affects approximately 36 million people worldwide[2]. The majority of these live in Sub-Saharan Africa. In South Africa there are approximately seven million people living with HIV[3]. In 2016 approximately 110 000 deaths in South Africa were attributed to HIV related conditions[2]. The condition affects both the health and wellbeing of individuals, but also society as a whole. Societal impacts include the disruption of family structures, increased social dependants such as orphans[2,3], loss of productivity[4], loss of tax income[4], and increased healthcare spending[5].

The effective control of the condition is predicated on consistent use of effective anti-retroviral treatment[6]. Inconsistent use or recurrent interruption of anti-retroviral therapy can lead to resistance developing to the treatment[1,7]. This means that it is important to investigate the reasons why patients are unable or unwilling to consistently take the prescribed medication.

The factors involved in determining compliance or causing treatment interruption are highly variable and dependant on the psychosocial circumstances of the individual. The reasons for non-compliance are usually grouped as patient related, socio-economic, medication, and healthcare and system factors[8]. These different factors will clearly play a variable role in each individual and will differ between communities. This necessitates investigating these causes in one's communities to be able to properly serve them.

The purpose of this research was to investigate the reasons cited for treatment interruption of anti-retroviral treatment in patients admitted to National district hospital from the Mangaung district where the healthcare workers are frequently confronted with the problem of non-adherence to ART.

Aims:

To investigate the reasons cited for treatment interruption of anti-retroviral treatment in patients admitted to National District Hospital from the Mangaung district; including medical, social and psychological factors.

Methodology:

Study Design:
The research was conducted in the form of an observational descriptive study. Data was quantitative in nature. The open-ended question where participants gave their own reason for treatment interruption was analysed and grouped into core themes (e.g., side effects related, lack of motivation etc.) after all data had been collected.

Study population:
Patients admitted to National Hospital adult wards (excluding the maternity ward), ages 18 and older who have been diagnosed HIV positive previously and had started treatment, but had interrupted treatment at the time of the study. Interruption was taken arbitrarily as any time that treatment was discontinued for 7 days or longer and not prescribed by a healthcare worker for a medical indication (e.g. as for example renal impairment). Patients were limited to those living in Bloemfontein and Mangaung district to limit variability in the group and maximise the potential for interventions to be tailored according to the community needs based on the findings of the research.
There were thought to be approximately 20 eligible patients who present to National District Hospital per week based on admission numbers from one week in 2019, this was later found to be an unrealistic figure, as the weekly number of eligible patients were found to be significantly less during the research period. Patients were identified by daily review of the newly admitted patients' files by the primary researcher. Some of these patients were inevitably unable to participate in the study due to the nature of their disease or non-consent.
As such the following patients were excluded:

- Delirium or GCS <15/15
- Declined consent for participation
- Unable to communicate due to severity of illness or comorbidities
- Patients unable to understand English, Afrikaans or Sotho.

However, if a patient was previously confused, but had become lucid, GCS 15/15, due to treatment, they were included into the study.

Estimated total number of study participants was planned to be 180. These numbers were not achieved due to reasons that will be discussed under limitations and a population of 17 participants was used.
A tally was also kept of the number of patients who met the inclusion criteria but did not participate due to the exclusion criteria or non-consent.

Measurements and data collection:
Data was collected by structured interviews administered by a research assistant who is a qualified nurse. Written consent was obtained from each eligible patient and the voluntary nature of the process was explained, as well as the fact that it would not influence their treatment.
The structured interview consisted of the research assistant reading the questions from a questionnaire to the participant and noting their answers on the applicable block. Answers were on a scale from 1 to 4, where 1 meant strongly disagree, 2 disagree, 3 agree, and 4 meant strongly agree as well as yes/no questions. There was also more exact data recorded such as participant income that was noted on the space provided. Open-ended questions at the start of the session allowed the participant to explain what they feel caused them to interrupt their ART. Structured interview format was chosen to facilitate faster interview process to include the maximal number of participants in the research, though this was later limited by the COVID-19 pandemic. It also allowed for a quantitative approach to the analysis of the

data. The questionnaire was developed specifically for this study based on the literature review's findings of the most common reasons for treatment interruption. The PHQ-9 screening tool was also included in the questionnaire as the link between depression and problems of forgetfulness, lack of motivation etc. are well documented and could play a significant role in. It was developed by the researcher (T.R. du Plessis) and reviewed by the consultants of the department of Family Medicine of the University of the Free State.
The interviews were conducted in English, Afrikaans or Sotho with questionnaires available in those three languages. These languages were chosen as they are the most commonly spoken languages in the Free State. The questionnaire's questions were available in the above languages, but answers were noted on the English version of the questionnaire that was handed in for analysis, thus limiting the number of different copies were needed to be made. The interviews took place in the most private facilities available in the ward that the patient was admitted in, this was pre-selected in each ward and organised with the matron of said ward. Instructions were also given on counselling the participants before the questionnaire session to facilitate an honest conversation free of actual or perceived judgement. There was also advisory literature available to the interviewer to reiterate these points.

PHQ-9[9] depression scale was used as a screening tool for symptoms of depression.

Pilot study:
A pilot study of 5 participants was conducted in a single ward at National District Hospital once approval had been obtained from the Health Sciences Research Ethics Committee and the relevant Hospital and Department of Health authorities. After the completion of the pilot study, the questionnaires, data form and data were analysed and feedback from research assistant evaluated to see if changes need to be made. Since the changes were limited and mostly corrections of errors identified on the format of the questionnaire, the data was included in the main research.

Statistical analysis:
The data was compiled by the researcher into a spreadsheet (Microsoft Excel) and statistical analysis was conducted by the department of Biostatistics of the University of the Free State.

Measurement and methodology errors:
Due to time constraints the questionnaire needed to be as concise as possible to facilitate the maximum number of participants. This meant that certain aspects may have been under or overestimated. Furthermore, complete screenings for symptoms of depression, for example, were not feasible in this context.

Biases may be introduced by the fact that the questionnaire was administered by a research assistant instead of self-administered. This loss of complete anonymity can influence the responses given. Participants may have felt self-conscious, or may have altered their reasoning to what they feel the interviewer would want. This was deemed the lesser bias as opposed to the loss of data from participants that are illiterate which could make the sample non-representative and would remove a particularly vulnerable group from the sample.

A suitable validated questionnaire that would have taken into account the psychosocial circumstances could not be found either, so this was the first time that this one was used. PHQ-9 was included in the questionnaire.

Results

Demographics are summarised in table 1.

Table 1: Demographics

Age (range)	18 to 72
Age (Median)	40
Male : female	7:10
Home language	Sotho 70%
	Afrikaans 18%
	Other 12%
Level of education	Range: no education to Gr 11 Gr 9 (Median)
Employment	Unemployed 68%
	Employed 32%

Reasons cited by patients for treatment interruption are summarised in Figure 1. Each participant could give more than one reason.

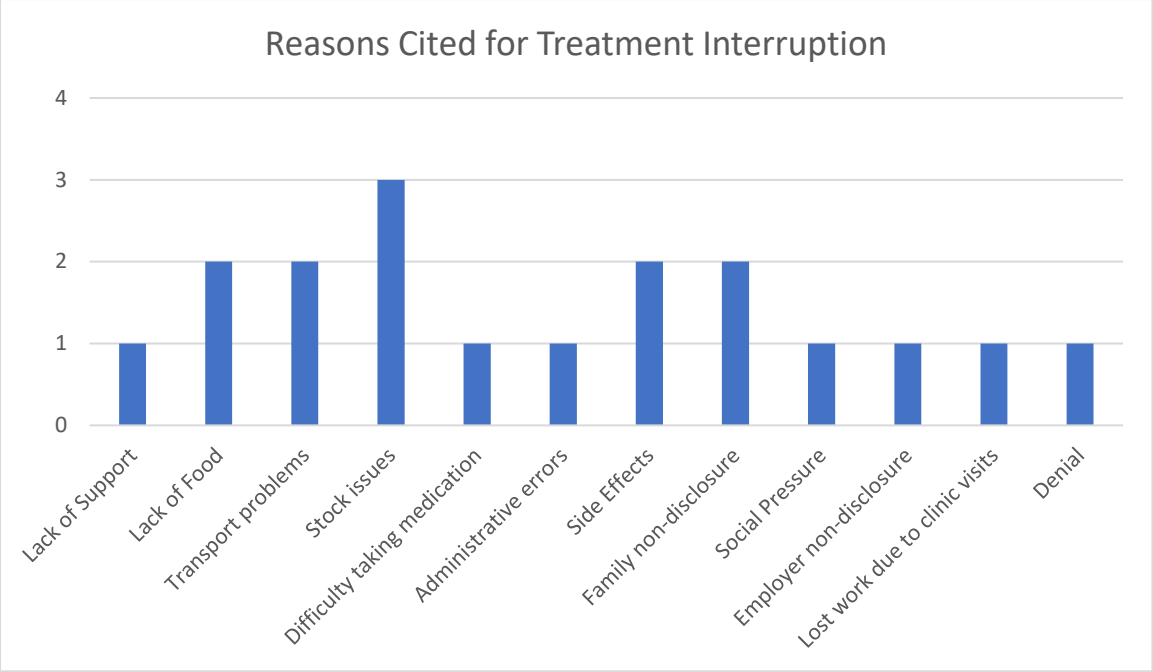

Figure 1: Reasons cited for treatment interruption

The median duration for treatment interruption was 7 months, but varied between one month and 6 years.

Almost 30 % (29.4%) of participants had defaulted treatment at least once before. With two participants having defaulted once before and two having defaulted three times before. One participant could not recall how many times he/she had defaulted.

Healthcare system factors:
The clinics where the participants used to follow up are listed in Table 2.

Table 2: Clinics where participants were followed up

Facility	Number of participants
Kagisanong	3
Mobile nr 6	1
Batho	1
Freedom Square	2
Gateway	1
Opkoms	1
Pelonomi (HCHC)	4
MUCPP	1
Thusong	1
Bainsvlei	1
Bloemspruit	1

Stock problems: 23% of participants reported being unable to obtain treatment due to stock issues.

Waiting times ranged from 2 to 48 hours, with a median of 5 hours. Seventeen percent of participants reported that waiting times contributed to their poor adherence (12% agreed, 5% strongly agreed).

Most participants (70%) felt that the clinic staff were supportive, of the remaining 30%, half strongly disagreed with the staff being supportive. There were 11% of participants who felt the lack of support from the clinic staff contributed to their non-adherence.

With regards to pre-ART counselling, 53% of the participants reported that they were counselled on all the relevant issues that the questionnaire enquired about. Seventeen percent answered no to all the questions regarding the topics they were counselled on. When looking at counselling around specific concepts, 23 % said they were not informed about the lifelong nature of ART, 17% about side effects they could expect, 35 % said they were not informed about ways of managing the side effects, and 23% reported the consequences of poor adherence were not explained to them.

Only one participant reported having moved to a new area, and said that it did not contribute to treatment interruption.

Medication:
The majority of patients (75%) took only one tablet per day with 6.25% taking two and four tablets per day and 12.5% taking three. Twelve percent of participants felt that the pill burden did contribute to their poor adherence.

Twenty five percent of participants reported forgetting to take their medication at times.

Negative side effects were experienced by 52% of participants. Of those, 44% reported that it contributed to their defaulting.

Ninety-four percent of participants reported that they no longer felt sick after taking their ART, and 20% reported that it contributed to them stopping their treatment.

Psychosocial:
With regards to transport to their clinic, 68% reported that it was regularly available. The majority of participants walked to the clinic (52%), thus not paying for transport. For the remainder of the participants the price of transport varied between R24 and R48, with a mean of R39.50. None of the participants felt that the cost associated with transport was contributing to their ART non-compliance.

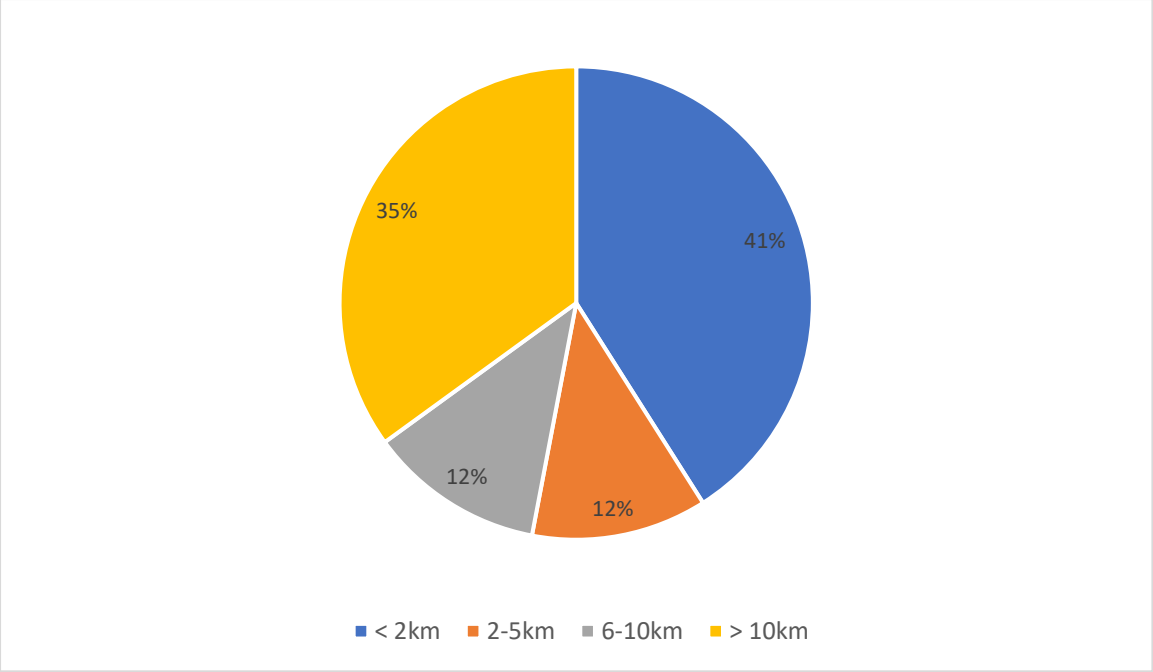

Figure 2: Distance from clinic

Fifty-three percent of participants reported that there are times when they do not have food to eat before taking their medication. Of those, 11% reported that it contributed to them defaulting their treatment.

None of the employed participants felt that their work obligations contributed to their adherence problems and all reported that their work afforded them time to attend clinic. This does however contradict some of their statements to the first question where loss of work was cited as a reason for treatment interruption.
Twelve percent of participants reported that they have not disclosed their HIV status to their families. All participants in relationships reportedly disclosed their status to their partners.

Ninety-three percent of patients reported that their families or partners were supportive. The 7 percent that reported their family is not supportive also indicated that this was a significant factor in their non-adherence.

Only 6 percent of participants worried that by attending clinic their HIV status may be implicitly disclosed to others. They did however say that this fear contributed to their non-adherence.

When asked about alcohol or drug use, 35% of participants reported using alcohol or drugs. Of these, 16% reported that it contributed to poor adherence.

Six percent of participants were receiving grants due to their health condition; however, they were not concerned that they might lose this grant if their health improved and it did not contribute to non-adherence.

The majority (54 percent) of participants reported no consistent income. The remainder had incomes in the range of R600 to R3000 per month. Most participants were unable to comment on their household incomes.

The daily use of ART was an unpleasant reminder of their condition to 18% of participants. Six percent of participants believe that traditional medicine or religious practice could cure HIV.

None of the participants had ever been targeted by criminals for their medication.

All participants scored at least 5 for their PHQ score indicating mild depression. The median score is 16 (scores between 15 and 19 indicate moderate to severe depression).

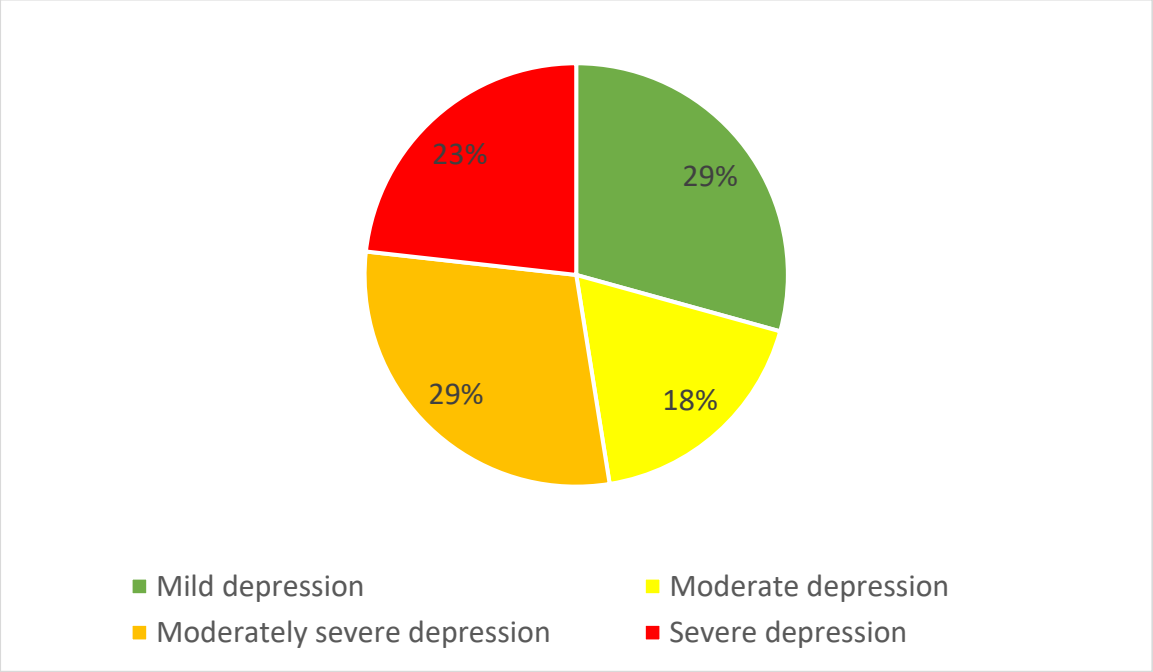

Figure 3: PHQ-9 classifications

Discussion

When looking at the demographics of the participants in this study multiple social problems become immediately clear. The lack of completed secondary education is deeply problematic. Education has a significant impact on multiple facets of life, all of which can influence adherence. The ability to understand the medication regime one is prescribed affects motivation and education level plays directly into the ability to understand and the ease with which these concepts can be explained by the healthcare workers. The further knock on effect can clearly be seen in the levels of unemployment faced by the participants. The implications of unemployment and poverty are far reaching. We will be exploring these factors further in the relevant sections.

With the knowledge that almost 30% of participants had previously defaulted their medication before the importance of properly finding the causative reason for the individual's adherence

difficulties is clear. The importance of adherence counselling is unquestioned, but there needs to be an emphasis placed on a collaborative process of individual problem identification and problem solving.

Healthcare system factors:
The issue of poor stock control, though not wide spread, had significant impacts on certain patients and one could extrapolate that it would have affected others within their communities as well. It shows the need for these problems to be timeously reported to the relevant authorities and the need for accountability within the system to ensure that patients have access to their treatment.

The overburdened healthcare system is clearly illustrated in the waiting times described by participants. When waiting times can account for almost an entire working day it is understandable that it can negatively affect compliance.

When it comes to the assessment of healthcare worker (HCW) supportiveness, it is reassuring that the vast majority of participants experienced good support. It is however worrying that many of the participants who felt that their HCWs were not supportive also cited this as a significant factor contributing to the defaulting of ART. This exemplifies the importance of the work done by the HCWs and the effect attitude can have. In this way one needs to shift one's focus to include factors that can affect the morale of HCWs and realise the impact that it can have down-stream in not only patient care, but also patient compliance.

Patient education has always been considered an important part of the consultation process. With that in mind, the results regarding patient pre-ART counselling is concerning. With just over half of participants having been informed of the four basic components enquired about in the questionnaire there is ample space for speculation regarding the other gaps in the patients ART education. The fact that there are participants who were not counselled on any of the factors is worrying. One does however have to keep in mind that patients may forget much of what is explained in a consultation, but, rather than excuse HCWs, it places emphasis on the continued education of patients. It also circles back to the concerns raised about the education level of the participants and the community as a whole.

The majority of patients did not report a significant pill burden. There is some concern that the question was misinterpreted as only referring to the number of ART tablets used. It is worth noting though, that increased number of tablets was reported by some of the participants as contributing to their defaulting and it highlights the need for careful consideration before prescribing more medication to patients as it may end up doing more harm than good, even if there are no pharmacological interactions.

The problem of medication side effects is illustrated in the results. With almost half of all the participants experiencing unpleasant effects and almost half of those saying that it played a role in their poor adherence it should sensitise us as HCWs to be empathetic to the difficulties facing the patients in this regard. It also again highlights the need to counsel patients on what can be expected and how to manage it. Conversely it is encouraging to see that most patients did feel healthier with their treatment, but the need for education regarding the importance of

continued compliance despite good health becomes clear when it contributes to the problem of non-compliance.

Psychosocial:
With regards to the role transport to clinics played in the problem, it is interesting to note that in this sample the price was rarely a contributing factor to non-adherence. The availability of reliable transport seemed to play a much larger role in the participants' inability to attend clinic. The value of having healthcare facilities near to patients is clear as it can have a direct impact on their ability to obtain their medication.

The problems of unemployment and poverty comes into stark relief when one considers that more than half of the participants reported no consistent income and often did not have food to eat before taking their treatment. It is actually surprising that it did not contribute to a larger proportion of the reason for non-compliance and seems to dispel the common attitude that non-compliance is a symptom of lack of discipline or resolve.

Some encouragement can be found in some of the data though. The stigma surrounding HIV seems to be less severe than reported in other studies as there are high rates of disclosure to family and partners, generally low fear of inadvertent disclosure through clinic attendance, and workplace support seems to be good. The value of this is also clear as when family support is lacking it contributed significantly to participant non-adherence.

Substance use or abuse was also reported less than expected and its influence on adherence was largely downplayed by participants. One can speculate about under reporting of alcohol or drug use due to social stigma. The effect of substance abuse on daily function may also be underemphasised due to psychological factors such as denial etc. These factors need to be considered when interpreting the findings but do remain largely speculative and the aim of the research remains to evaluate the reasons cited for non-adherence and not necessarily a root cause analysis.

The low percentage of participants who believed traditional medicine or religious practice would cure their HIV could be reflective of the urbanised nature of the communities sampled and also the effect of the years of government education programs.

By far the most striking finding of this research is the results of the PHQ-9 questionnaire. Though this is merely a screening tool and not diagnostic, it remains a validated measure for evaluating depression. The fact that all of the participants were classified into one of the levels of depression shows the pervasive nature of the problem. The large number of participants that scored moderate up to severe is troubling. It is largely unsurprising that this is what was found considering the social and health situations that many of them come from, but the sheer number and the severity of the symptoms remain problematic. Depression can affect almost all aspects of life and could definitely impact on treatment adherence. It seems prudent then that the PHQ-9 or similar questionnaire might be implemented during the drug readiness training that pre-ART patients undergo, to screen for signs and symptoms of depression. These findings also beg the question about mental health in the general population of the community. Further

research into the prevalence of depression in the community can bring valuable insights and possibly help bring attention to the problem.

The most prominent limitation of this study is the small number of research participants. This came about due to multiple factors.

The first factor was the initial over estimation of the number of patients that are admitted with the inclusion criteria. The estimation was based on a record of the number of patients admitted to the wards of National hospital in a one-week period in August 2019. The over estimation was due to the initial estimation of weekly potential participant admissions not taking into account how many patients were not from the Mangaung district, the number of patients not meeting inclusion criteria for other reasons (low GCS etc.) and the variability of admissions on a week to week basis.

The second factor was the COVID-19 pandemic and associated lockdown measures. Even prior to the official initiation of lockdown, it was decided to pause continued data collection for the safety of the research assistant as she made use of public transport. With the continued worsening infection rates of COVID-19 the decision was made by the researcher to attempt the data collection via telephonic interview, but this was unacceptable to the research assistant.

Due to the time constraints of the MMED program and clinical work the decision was made to halt the data collection at that point as was discussed with HSREC and the research supervisor. Further limitations include the variety of communities within the Mangaung metro that end up being evaluated. This can be seen as a positive aspect; it shows a greater continuum of experiences and factors that can affect adherence, but conversely it diminishes the ability to identify specific problems within a certain area.

Limitations

The most prominent limitation of this study is the small number of research participants. This came about due to multiple factors.
The first factor was the initial over estimation of the number of patients that are admitted with the inclusion criteria. The estimation was based on a record of the number of patients admitted to the wards of National hospital in a one-week period in August 2019. The over estimation was due to the initial estimation of weekly potential participant admissions not taking into account how many patients were not from the Mangaung district, the number of patients not meeting inclusion criteria for other reasons (low GCS etc.) and the variability of admissions on a week to week basis.

The second factor was the COVID-19 pandemic and associated lockdown measures. Even prior to the official initiation of lockdown, it was decided to pause continued data collection for the safety of the research assistant as she made use of public transport and had multiple risk factors for severe COVID-19. With the continued worsening infection rates of COVID-19 the decision was made by the researcher to attempt the data collection via telephonic interview, but this was unacceptable to the research assistant.

Due to the time constraints of the MMED program and clinical work the decision was made to halt the data collection at that point as was discussed with HSREC and the research supervisor. Further limitations include the variety of communities within the Mangaung metro that end up being evaluated due to National District Hospital serving all these different communities. This can be seen as a positive aspect; it shows a greater continuum of experiences and factors that can affect adherence, but conversely it diminishes the ability to identify specific problems within a certain area.

Conclusion:

The challenges for people living with HIV to remain compliant with their treatment remains numerous and varied. The role that unemployment and poverty plays cannot be ignored. Despite improved access for impoverished people to anti-retroviral therapy, the socio-economic context remains problematic to treatment adherence.

Continuing efforts need to be made to create a robust supply of medication to patients if good outcomes are to be achieved. The healthcare system should not be the cause for treatment interruption in otherwise motived patients.

Patients need to be well educated prior to treatment initiation and given good advice regarding the management of side effects. Hopefully as ART development continues our regimens will give less unpleasant side effects.

The prevalence of symptoms of depression in this patient population is alarming and needs to be actively screened for at initiation and follow-up of patients.

The limited effects of stigma and victimisation reported in this research shows that there is progress being made with this regard.

Further research within more well-defined communities can be beneficial for the healthcare workers working in those areas. Larger patient numbers will help to paint a better picture of the individual communities and the prominent challenges they face. It is hoped that these results will inspire empathy and compassion towards this patient population as a whole.

References:

1. Davidson, S. S. (2010). Davidson ’ s Medicine. In *Davidson’s principles and practice of medicine*.
2. UNAIDS. (2017). Fact sheet - Latest global and regional statistics on the status of the AIDS epidemic. https://doi.org/2017
3. Statistics SA. (2018). Mortality and causes of death in South Africa, 2016: Findings from death notification. In *Statistical release P0309.3*. https://doi.org/Statistical release P0309.3

4. Ellis, L. L., Smit, B. W., & Laubscher, P. (2003). The Macro-economic Impact of HIV/AIDS in South Africa. *Journal for Studies in Economics and Econometrics*, *27*(2), 1–28.
5. National Treasury of South Africa. (2018). *Budget Review 2018*.
6. Bor, J., Herbst, A. J., Newell, M. L., & Bärnighausen, T. (2013). Increases in adult life expectancy in rural South Africa: Valuing the scale-up of HIV treatment. *Science*. https://doi.org/10.1126/science.1230413
7. Gardner, E. M., Sharma, S., Peng, G., Hullsiek, K. H., Burman, W. J., MacArthur, R. D., … Mannheimer, S. B. (2008). Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance. *AIDS*. https://doi.org/10.1097/QAD.0b013e3282f366ff
8. Azia, I. N., Mukumbang, F. C., & Van Wyk, B. (2016). Barriers to adherence to antiretroviral treatment in a regional hospital in Vredenburg, Western Cape, South Africa. *Southern African Journal of HIV Medicine*. https://doi.org/10.4102/sajhivmed.v17i1.476
9. Kroenke, K., Spitzer, R. L., & Williams, J. B. W. (2001). The PHQ-9: Validity of a brief depression severity measure. *Journal of General Internal Medicine*. https://doi.org/10.1046/j.1525-1497.2001.016009606.x

Appendices

Appendix A: Letter of approval from Health Sciences Research Ethics Committee

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

Health Sciences Research Ethics Committee

06-Jan-2020

Dear **Dr Thomas Du Plessis**

Ethics Clearance: **Reasons Cited for the Interruption of Anti-Retroviral Treatment in the Bloemfontein/Mangaung Area**
Principal Investigator: **Dr Thomas Du Plessis**
Department: **Family Medicine Department (Bloemfontein Campus)**
APPLICATION APPROVED

Please ensure that you read the whole document

With reference to your application for ethical clearance with the Faculty of Health Sciences, I am pleased to inform you on behalf of the Health Sciences Research Ethics Committee that you have been granted ethical clearance for your project.

Your ethical clearance number, to be used in all correspondence is:**UFS-HSD2019/1575/2801**

The ethical clearance number is valid for research conducted for one year from issuance. Should you require more time to complete this research, please apply for an extension.

We request that any changes that may take place during the course of your research project be submitted to the HSREC for approval to ensure we are kept up to date with your progress and any ethical implications that may arise. This includes any serious adverse events and/or termination of the study.

A progress report should be submitted within one year of approval, and annually for long term studies. A final report should be submitted at the completion of the study.

The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

For any questions or concerns, please feel free to contact HSREC Administration: 051-4017794/5 or email EthicsFHS@ufs.ac.za.

Thank you for submitting this proposal for ethical clearance and we wish you every success with your research.

Yours Sincerely

Dr. SM Le Grange
Chair : Health Sciences Research Ethics Committee

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | E: ethicsfhs@ufs.ac.za
IRB 00006240; REC 230408-011; IORG0005187; FWA00012784
Block D, Dean's Division, Room D104 | P.O. Box/Posbus 339 (Internal Post Box G40) | Bloemfontein 9300 | South Africa
www.ufs.ac.za

Appendix B: Participant information form

Study: Reasons cited for ART treatment interruption in the Bloemfontein/Mangaung area:

Principal researcher: Dr Ross du Plessis

Dear participant

We are conducting research with regards to the reasons why patients on ART (anti-retroviral treatment) stop taking their medication. This is an important problem in our communities and it is one that is often poorly understood. Continued compliance to ART is often challenging for a number of different reasons, but we want to hear from you what was the factors that influenced you to interrupt your treatment regimen. We need this information to be able to improve the systems that you and others use so that we can prevent the serious problems associated with irregular ART use.
The research process will involve a research assistant asking you a series of questions related to the health care system, the medication you use, your social circumstances and psychological factors. It also includes screening questions for depression. Should it become apparent that you might have depression, further evaluation and treatment will be offered to you.
All the information gathered in this study will be anonymous and no one will be able to find out which answers were yours. Participation in the study is also completely voluntary and you will not be treated any differently should you decide not to participate. There will be no payment or remuneration for participation.
I hope you will help us with this important work.

Thank you in advance

Dr Ross du Plessis

MbChB(UFS)
Family medicine registrar

Principal researcher

Health science research ethics committee contact details:

E-Mail: EthicsFHS@ufs.ac.za

Mrs Maré Marais (Head of Ethics Administration)
Telephone: 051 401 7795

Appendix C: Participant consent form

Consent form:
Study: Reasons cited for ART (anti-retroviral treatment) interruption in the Bloemfontein/Mangaung area
Principal researcher: Dr. Ross du Plessis

Research Consent:

Dear Participant, we are conducting research to find out what the main reasons are why people are having difficulty taking their HIV medication continuously. For this we need your help to tell us about the challenges you faced and what the reasons were that you were unable to continue with the medication. The goal of this is so that we can identify the problems that our community faces and then create and implement plans to help relieve those problems. Your participation in this research is important to help us achieve this. The choice to participate is yours, and you choosing to participate or not will not affect your treatment at all. You also have the choice to stop participating at any time. Your name, or any identifying information will not be written down, so no one will know the information given is yours. You will be anonymous.
You will be expected to answer a series of questions asked by a doctor or nurse regarding your experiences with the health care system, problems encountered with the medication as well as social and psychological factors that could influence adherence to the medication. There will also be a part of the questionnaire that will screen for symptoms of depression. If there are symptoms of depression present, we will, with your permission, inform your treating doctor of the possibility that you may be suffering from depression.
You will have the opportunity to tell us about other factors that you feel influenced you to stop taking the medication.
This process should not take longer than 15minutes.

Should you want any more information, please contact Ross du Plessis (principal researcher) on 072 495 9164

If you choose to participate, please sign and date below:

_____ _____

Signature Date (dd/mm/yy)

Appendix D: Permission from Free State Department of Health

health
Department of Health
FREE STATE PROVINCE

04 December 2019

Dr T Du Plessis
Dept. of Family Medicine
UFS

Dear Dr T Du Plessis

Subject: Reasons cited for the interruption of Anti-Retroviral Treatment in the Bloemfontein/Mangaung Area.

- Please ensure that you read the whole document. Permission is hereby granted for the above – mentioned research on the following conditions:
- Participation in the study must be voluntary.
- A written consent by each participant must be obtained.
- Serious Adverse events to be reported to the Free State department of health and/ or termination of the study
- Ascertain that your data collection exercise neither interferes with the day to day running of **National Hospital** nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and please do not obtain information regarding the identity of the participants.
- **Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).**
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** sebeelats@fshealth.gov.za / makenamr@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- **Please discuss your study with Institution Manager on commencement for logistical arrangements see 2nd page for contact details.**
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- **As part of feedback you will be required to present your study findings/results at the Free State Provincial health research day**

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 5/12/19

Head : Health
PO Box 227, Bloemfotein, 9300
4th Floor, Executive Suite, Bophelo House, cnr Maitland and, Harvey Road, Bloemfotein
Tel: (051) 408 1646 Fax: (051) 408 1556 e-mail:khusemj@fshealth.gov.za@fshealth.gov.za/chikobvup@fshealth.gov.za

Appendix E: Copy of the research protocol approved by the HSREC

Reasons Cited for the Interruption of Anti-Retroviral Treatment in the Bloemfontein/Mangaung Area

Thomas Ross du Plessis

Index:

Researchers:

Dr. Ross du Plessis
MBChB(UFS) , MP0784265
Registrar in Family Medicine
University of the Free State
Student Nr 200701930
072 495 9164
Ross.duples@gmail.com

Dr M. van Lill
MBChB, M.Med (Fam)
Consultant family physician
University of the Free State

Introduction:

The human immunodeficiency virus (HIV) is a retrovirus that targets human CD4 leukocytes as its site of replication(1). Via reverse transcriptase enzymes the virus incorporates its genes into the DNA of the leukocyte thereby causing it to continually produce copies of the virus and its associated proteins(1). This process is prone to errors and thus produces numerous genetically heterogenic versions of the virus due to the resultant mutations. This means that the virus has the potential for rapid development of resistance when the viral replication is not suppressed. The infection causes a progressive immune deficiency by among other mechanisms the destruction of CD4 cells as well as the demodulation of the immune system(1). It is also associated with numerous other complications including renal disease, vasculitis, venous thrombosis and thromboembolism, cerebrovascular accident, cancers and auto immune conditions(1). It is predominantly spread through sexual transmission, but can be transmitted through needle sharing or through other body fluids such as blood coming in contact with broken mucous membranes or skin.
HIV infection is a major cause of concern internationally, with approximately 36 million people living with the condition worldwide, but even more so in sub-Saharan Africa and specifically in South Africa. According to statistics SA, approximately 12.6% or 7.1 million of South Africa's population is living with HIV(2). In the 15-59 age group the prevalence is even higher at 18%. The infection rate among women is higher still, with many pregnant women being infected. 56% of the population living with HIV are on ART as of 2016, with a 95% treatment rate for pregnant females(3). According to UNAIDS, 110 000 deaths in 2016 in South Africa could be attributed to HIV(2).

On a societal level the pandemic has many effects. The number of people who are dependent on external support increases as people become too ill to take care of themselves and their families, orphans end up increasingly as the heads of families attempting to make ends meet. The fact that the highest prevalence occurs in the working age group(2,3) means that there is a direct impact on the work force and productivity. This means loss of gross domestic production and tax revenue for the country as well as the damages to the individual businesses with work days lost due to frequent illness or the loss of workers due to HIV related deaths(4). The South African government has budgeted R205Bn for the department of health, with R66.4Bn allocated to the treatment and prevention of HIV(5). This does not account for the further increase cost in hospitalization and treatment of infection and other health impacts of HIV (for example cerebrovascular accidents, lymphoma, Kaposi sarcoma etc.) There are approximately 1.3 million AIDS orphans in South Africa as of 2016 placing a severe strain on the social services of the country(2).
The burden of HIV and AIDS has been significantly decreased with the use of effective ART as well as progressively more inclusive guidelines for ART initiation. This has increased life expectancy and decreased morbidity leading to generally longer lives with fewer complications(3,6). New HIV infections peaked in 1998 with an estimated 560 000 people being infected with the condition in that year; the estimate for 2016 is down to 270 000. The number of people living with the condition is still increasing though as the infection rate is

still considerably higher than the death rate which has been steadily improving thanks to the measures that have been implemented. The peak of annual deaths was in 2006 with an estimated 280 000 people dying because of the disease(2).

On a personal level HIV infection is associated with deteriorating functional status due to opportunistic infections and HIV wasting syndrome. It also carries with it significant emotional problems as patients experience the stigma associated with the illness as well as the depression and anxiety that so called "dread diseases" carry with them. Interpersonal relationships can be significantly complicated due to the condition, especially in cases of discordant couples(7). HIV infected people were found to be poorer than those living without HIV and were generally ill more of the time(8). These factors have been shown to have a significant impact on patient adherence to ART. Patient personality has been shown to affect adherence and it has been shown that treating depression has a significant effect on improving adherence to ART(9,10).
Good compliance to ART has been shown to improve patient outcomes(6): with sufficient adherence to highly active anti-retroviral treatment viral replication in CD4 cells can be suppressed. This leads to decreased viral loads and improved CD4 counts. As the immune function improves, the incidence of opportunistic infections decreases leading to improved quality of life and general function. Especially important in the South African setting is the improved resilience to tuberculosis infection, a leading cause of death and morbidity.
Poor adherence to ART is associated with diminishing immune function and opportunistic infections as well as HIV treatment resistance(1,11). This leads to increased viral loads in patients which in turn increases the likelihood of transmission of the infection both in mother to child transmission and to sexual partners(12). With unsuppressed viral loads the patient's CD4 count and immune function will progressively decline as the virus replicates.

The importance of ensuring proper adherence to ART is thus obvious, but how can we assist patients in taking their medication consistently? To answer this question, we first need to find out what are the factors that is influencing treatment adherence. This is clearly a multifactorial problem that likely will have causes that will be specific to the community that is being serviced as well as broader themes that can be found in other studies. Previous studies looking at the barriers to adherence uncovered larger themes or classes of problems that can be explored. These are typically classified as:

5. Patient related
6. Socio-economic
7. Medication
8. Health care team and system

Under these headings the specific problems can be subdivided and assessed. Issues that have been identified by previous studies under these headings include:

Patient related:
Experiencing better health(13):
Some patients reported that once their health had improved, they tended to forget to take their treatment as their symptoms that reminded them that they are sick were no longer there.

Forgetfulness(13):
Unintentional missing of doses due to their mind being occupied by other concerns.
Pessimism/depression(9,10,13):
Some patients actually stop their treatment with the reported intent as a means to end their lives.
Emotional distress(13):
During emotional crisis patients reported that they would often neglect to take their treatment
Alcohol or drug use(13–16)
Religious or cultural(13,15,16):
Some patients reported that they would rather use traditional medicine or that their faith would cure them.

Socio-economic:
Lack of money for food(13,17)
Unable to afford transport(13,18)
Disability grants(13):
Some patients would stop taking treatment in the hope of obtaining a grant once they are ill
Stigma(13)
Fear of disclosure(13,19)

Medication related:
Side effects(13,16):
Patients reported that they would stop treatment as they could not cope with the side effects
Pill burden(20):
This was a prominent factor in patients who had to take HAART as well as treatment for other conditions such as TB.

Health care team and system:
Poor patient education(13,15):
Patients not adequately trained on how to take their medication
Follow up scheduling(13):
Sometimes patient follow ups are scheduled for a longer time period than their medication would last them
Breakdown of patient-carer relationship(15):
Patients lost trust in the medical and nursing staff at the clinics due to the way they were treated
Long Waiting times and overcrowding(15,16)
Working hours of facilities(15)

It is clear how much variety there is to the reasons why each individual patient may interrupt their ART, thus it becomes very important to understand the main factors prevalent in the communities one serves especially from the point of view of family medicine and community

oriented primary care. Only once a proper understanding of the problems has been gained can one develop plans to address them.

Aim:
To investigate the reasons cited for treatment interruption of anti-retroviral treatment in patients admitted to National District Hospital from the Mangaung district.

Methodology:
Study Design:
The research will be conducted in the form of an observational descriptive study. Data will be quantitative in nature. The open-ended question where participants are to give their own reason for treatment interruption will be analysed and grouped once all data has been collected.

Study population:
Patients admitted to National Hospital adult wards, ages 18 and older who have been diagnosed HIV positive previously and had started treatment, but have currently interrupted treatment. Interruption will be taken arbitrarily as any time that treatment was stopped for 7 days or longer that was not prescribed by a healthcare worker for a medical indication (e.g. renal impairment). Patients will be limited to those living in Bloemfontein and Mangaung to limit variability in the group and maximise the potential for interventions to be tailored according to the community needs based on the findings of the research.
There are approximately 20 eligible patients who present to National District Hospital per week. Some of these patients will inevitably be unable to participate in the study due to the nature of their disease or non-consent.
As such the following patients will be excluded:

- Delirium or GCS <15/15
- Declined consent for participation
- Unable to communicate due to severity of illness or comorbidities
- Patients unable to understand English, Afrikaans or Sotho.

If however a patient was previously confused, but has become lucid, GCS 15/15, due to treatment, they can be included into the study.

Estimated total number of study participants is 180.
A tally will also be kept of the number of patients who meet the inclusion criteria but did not participate due to the exclusion criteria or non-consent.

Measurements and data collection:
Data will be collected by structured interview administered by a research assistant who is a qualified nurse. Written consent will be obtained from each eligible patient and voluntary nature of process explained as well as the fact that it will not influence their treatment.
The structured interview consists of the research assistant reading the questions from a questionnaire to the participant and noting their answers on the applicable block. Answers will be on a scale from 1 to 4, where 1 means strongly disagree, 2 disagree, 3 agree, and 4

means strongly agree as well as yes/no questions. There will also be more exact data recorded such as income that will be noted on the space provided. There will also be open-ended questions at the start of the session to allow the participant to explain what they feel caused them to interrupt their ART. The questionnaire was developed specifically for this study based on the literature review's findings of the most common reasons for treatment interruption.
The interviews will be conducted in English, Afrikaans or Sotho with questionnaires available in those three languages. The questionnaire's questions will be available in the above languages, but answers will be noted on the English version of the questionnaire that will be handed in for analysis, thus limiting the number of different copies needed to be made. The interviews will take place in the most private facilities available in the ward that the patient is admitted in, this will be pre-selected in each ward and organised with the matron of said ward. Instructions will also be given on counselling the participants before the questionnaire session to facilitate an honest conversation free of actual or perceived judgement. There will also be advisory literature available to reiterate these points.
The questionnaire will record demographic data, including the suburb or district where the participant lives, but not the actual street address. Furthermore, the forms will be kept confidential, with only a number assigned to each form to ensure that data forms can be checked with regards to the data entered. Data forms/questionnaires will be handed in by the research assistant directly to the principle researcher to ensure confidentiality is maintained.
PHQ-9(21) depression scale will be used as a screening tool for symptoms of depression. Answers are scored 0 to 3 (not at all= 0, nearly every day=3). Any scores between 5-9 indicate mild depression, 10-14 moderate depression, 15-19 moderately severe depression and 20-27 indicates severe depression. Any score of 5 or more should be relayed to the treating physician with the participant's permission.

Pilot study:
A pilot study of 5 patients will be conducted in a single ward at National district hospital once approval has been obtained from the Health Sciences Research Ethics Committee and the relevant Hospital and Department of Health authorities. After the completion of the pilot study the questionnaires, data form and data will be analysed and feedback from research assistant evaluated to see if changes need to be made. If there are no changes made, or of limited scope, the data will be included as part of the final study.

Statistical analysis:
The data will be compiled by the researcher into a spreadsheet (Microsoft Excel) and statistical analysis will be conducted by the department of Biostatistics of the University of the Free State.

Measurement and methodology errors:

Due to time constraints the questionnaire needed to be as concise as possible to facilitate the maximum number of participants. This means that certain aspects may be under or overestimated. Furthermore, complete screenings for symptoms of depression, for example,

are not feasible in this context.
Biases may be introduced by the fact that the questionnaire is administered by a research assistant instead of self-administered. This loss of complete anonymity can influence the responses given. Participants may feel self-conscious, or may alter their reasoning to what they feel the interviewer would want. This was deemed the lesser bias as opposed to the loss of data from participants that are illiterate which could make the sample non-representative and would remove a particularly vulnerable group from the sample.
A suitable validated questionnaire that would take into account the psychosocial circumstances could not be found either, so this is the first time that this one will be used. PHQ-9 is included in the questionnaire.

Ethical considerations:

The research protocol will be evaluated by the Health Science Research Ethics Committee and research will only be started once approval has been obtained.

Due to the sensitive nature of the information being obtained with this research confidentiality is paramount. The importance of this will be pressed upon all those who act as interviewers.
Almost synonymous with the need for confidentiality is the need for privacy during the interviews. All reasonable efforts will be expended to ensure that the interviews are conducted in locales that are suitably private and free of interference. As stated before, all questionnaires and data forms will remain confidential and be kept under lock and key.
The stress placed upon the participants needs to be considered as many of the questions are deeply personal. The importance of a welcoming, non-judgemental interviewer and environment will be stressed to the interviewers. Further referral to psychology and treatment will be offered to those who score highly on the depression screening questions.

Implementation of Findings:

The findings of this research will be used as part of MMED(Fam) dissertation and will be submitted for publication.
The findings of this research will hopefully be useful for individual practitioners working with these patients as well as to the district health authorities. For the practitioners it will be useful in identifying risk factors for treatment interruption in their patients and help them to be able to attempt to put in place plans to mitigate the risk. It will also assist them in having a better understanding of what is motivating patients to default their treatment and the challenges their patients face. This can potentially boost empathy and patient-healthcare worker relationships.
On district level I hope that this research will help inform the authorities about which factors are driving the problem of ART non-adherence so that policies and interventions may be developed to decrease this significant problem. It can also form a good point of reference from which to evaluate the impact of strategies implemented to improve adherence.
I also believe that the findings will be of use to the wider medical community in South Africa

as well, to illustrate the possible stumbling blocks present in similar communities and to hopefully inspire further research in the topic. If the questionnaire is adopted or used in other communities it could improve our understanding of wider trends in non-compliance, effectively building a map of where which factors are contributing to all the problems associated with poor compliance.

Time Line:

References:

1. Davidson SS. Davidson ' s Medicine. Davidson's principles and practice of medicine. 2010. 384–408 p.
2. UNAIDS. Fact sheet - Latest global and regional statistics on the status of the AIDS epidemic. UNAIDS Fact Sheet 2017. 2017.
3. Statistics SA. Mid year population estimates. Vol. 8. 2018.
4. Ellis LL, Smit BW, Laubscher P. The Macro-economic Impact of HIV/AIDS in South Africa. J Stud Econ Econom. 2003;27(2):1–28.
5. National Treasury of South Africa. Budget Review 2018. 2018.
6. Bor J, Herbst AJ, Newell ML, Bärnighausen T. Increases in adult life expectancy in rural South Africa: Valuing the scale-up of HIV treatment. Science (80-). 2013;
7. Romel D. Mackelprang, Rose Bosire Brandon L. Guthrie, Robert Y. Choi, Amy Liu, Anne Gatuguta, Anne F. Rositch, James N. Kiarie CF. High rates of relationship dissolution among HIV-serodiscordant couples in Kenya. AIDS Behav. 2014;18(1):189–93.
8. Bachmann MO, Booysen FLR. Health and economic impact of HIV/AIDS on South African households: A cohort study. BMC Public Health. 2003;3:1–8.
9. Moosa MYH, Jeenah FY. Treating depression in HIV-positive patients affects adherence. South Afr J HIV Med. 2017;13(3):144–9.

10. O'Cleirigh C, Ironson G, Weiss A, Costa PT. Conscientiousness Predicts Disease Progression (CD4 Number and Viral Load) in People Living With HIV. Heal Psychol. 2007;26(4):473–80.

11. Gardner EM, Sharma S, Peng G, Hullsiek KH, Burman WJ, MacArthur RD, et al. Differential adherence to combination antiretroviral therapy is associated with virological failure with resistance. AIDS. 2008;

12. Attia S, Egger M, Müller M, Zwahlen M, Low N. Sexual transmission of HIV according to viral load and antiretroviral therapy: Systematic review and meta-analysis. Aids. 2009;23(11):1397–404.

13. Azia IN, Mukumbang FC, Van Wyk B. Barriers to adherence to antiretroviral treatment in a regional hospital in Vredenburg, Western Cape, South Africa. South Afr J HIV Med. 2016;

14. Begley K, McLaws ML, Ross MW, Gold J. Cognitive and behavioural correlates of non-adherence to HIV anti-retroviral therapy: Theoretical and practical insight for clinical psychology and health psychology. Clin Psychol. 2008;12(1):9–17.

15. Kip E, Ehlers VJ, Van Der Wal DM. Patients adherence to anti-retroviral therapy in Botswana. J Nurs Scholarsh. 2009;41(2):149–57.

16. Dahab M, Charalambous S, Hamilton R, Fielding K, Kielmann K, Churchyard GJ, et al. "That is why I stopped the ART": Patients' & providers' perspectives on barriers to and enablers of HIV treatment adherence in a South African workplace programme. BMC Public Health. 2008;8:1–6.

17. Weiser SD, Tuller DM, Frongillo EA, Senkungu J, Mukiibi N, Bangsberg DR. Food insecurity as a barrier to sustained antiretroviral therapy adherence in Uganda. PLoS One. 2010;5(4).

18. J.S. M, L. I, F. L, P. F, H. B. Antiretroviral therapy in resource-poor settings: Decreasing barriers to access and promoting adherence. J Acquir Immune Defic Syndr [Internet]. 2006;43(SUPPL. 1):S123–6. Available from: http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed7&NEWS=N&AN=2006602950

19. Rodger AJ, Lascar M, Collins S, Perry N, Daskalopoulou M, Wilkins E, et al. Non-Disclosure of HIV Status and Associations with Psychological Factors, ART Non-Adherence, and Viral Load Non-Suppression Among People Living with HIV in the UK. AIDS Behav. 2016;21(1):184–95.

20. Ruanjahn G, Roberts D, Monterosso L. An exploration of factors influencing adherence to highly active anti-retroviral therapy (HAART) among people living with HIV/AIDS in Northern Thailand. AIDS Care - Psychol Socio-Medical Asp AIDS/HIV. 2010;22(12):1555–61.

21. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: Validity of a brief depression severity measure. J Gen Intern Med. 2001;

Appendix F: Questionnaire

Questionnaire: Questionnaire Nr:_____

Date
_____ (dd/mm/yy)

Interviewer:
_____

Please complete in the available spaces or mark the appropriate option with an X:

Demographics:
Age: _____(years)

Sex: Male Female

Home Language:
Sotho English Afrikaans Other: _____
Education level (highest level completed):
None Highest School grade achieved: Gr_____ Tertiary diploma or degree

Employment:
Unemployed Piece Jobs Other Specify:_____

Area of residence: _____ (suburb only e.g. Phase 9/Rocklands)

Participant's reason:

1. What do you feel caused you to stop taking your ART?

_____
_____
_____
_____
_____
_____
_____

Adherence:
2.1 When did you first start your ART: _____(mm + yyyy)
2.2 How long have you **not** been taking your ART now?
_____(specify weeks/months/years)
2.3 Has there been previous times when you stopped taking your ART medication for more than a week?
Yes No
2.4 If answered yes to 2.3, how many times? ___

Healthcare System Factors:

3.1Which facility do you receive your medication from? _____

3.2Has there been times when you could not take your ART because your clinic did not have stock of it?

Yes No

3.3 How long do you wait to get medication from your facility?

_____ hours

3.4 Has the waiting times contributed to you stopping your medication?

Strongly disagree Disagree Agree Strongly agree

3.5 Are the healthcare workers at your facility supportive?

Strongly disagree Disagree Agree Strongly agree

3.6 If you feel the health care workers are not supportive, do you think this contributed to you stopping your medication?

Strongly disagree Disagree Agree Strongly agree

3.7 Was it explained that you would need to take ART for the rest of your life before you were started on your treatment?

Yes No

3.8 Did they explain possible side effects to you before the treatment was started?

Yes No

3.9 Did they explain possible ways of coping with the side effects?

Yes No

3.10 Did they explain the consequences of stopping your ART?

Yes No

3.11 Did you move to a new area?

Yes No

3.12 If "yes" to 3.11, did you have difficulties to obtain your ART from the clinic in your new area?

Yes No

Medication related:

4.1 How many tablets did you have to take each day? ____

4.2 Do you feel that having to take many tablets made it difficult to keep taking them regularly?

Strongly disagree Disagree Agree Strongly agree

4.3Did you sometimes have trouble remembering to take the tablets every day?

Strongly disagree Disagree Agree Strongly agree

4.4 Did you experience unpleasant side effects when taking the medication?

Yes No

4.5 If yes to 4.4, did this contribute to you stopping to take the medication?

Strongly disagree Disagree Agree Strongly agree

4.6 Did you no longer feel sick while being on the ART?

I still felt sick | I no longer felt sick

4.7 Do you think this contributed to you no longer taking your ART?

Strongly disagree | Disagree | Agree | Strongly agree

Psychosocial:

5.1 Is transport readily available from your home?

No | Yes

5.2 How much does transport cost you to and from the facility/clinic per visit?

R_____

5.3 Do you feel this cost contributed to you stopping your ART?

Strongly disagree | Disagree | Agree | Strongly agree

5.4 Approximately how far is your healthcare facility from your home?

<2km | 2-5km | 6-10km | >10km

5.5 Are there times when you do not have food to eat before taking your ART?

Yes | No

5.6 If yes to 5.5, do you feel this contributed to you stopping your treatment?

Strongly disagree | Disagree | Agree | Strongly agree | N/A

5.7 If employed, do you feel your work obligations affected your ability to attend clinic / obtain ART?

Strongly disagree | Disagree | Agree | Strongly agree | N/A

5.8 If employed, did your employer afford you time to attend clinic / obtain treatment?

No | Yes | N/A

5.9 If "No" to 5.8, do you think this contributed to you stopping your ART?

Strongly disagree | Disagree | Agree | Strongly agree | N/A

5.10 Does your family know of your HIV diagnosis?

Yes | No

5.11 Does your current partner know of your HIV diagnosis?

Yes | No | Single

5.12 If "No" to 5.10 and/or 5.11, did you have to hide the fact that you needed to take medication or go to the clinic?

Yes | No | N/A

5.13 If "yes" to 5.12, do you think this contributed to you stopping to take your ART?

Strongly disagree | Disagree | Agree | Strongly agree

5.14 If "Yes" to 5.10 and/or 5.11, did your family/partner support you in taking your ART?

Yes | No

5.15 Did you worry that by going to the healthcare facility/clinic other people might find out about your HIV status?

Strongly disagree | Disagree | Agree | Strongly agree

5.16 If "Agree/strongly agree" to 5.15, do you think this contributed to you stopping to take your ART?

Strongly disagree | Disagree | Agree | Strongly agree

5.17 Do you take any alcohol and/or drugs?

Yes | No

5.18 If "yes" to 5.17, do you feel this contributed to you stopping to take your ART?

Strongly disagree | Disagree | Agree | Strongly agree | N/A

5.19 Did you receive any grants because of your HIV status?

Yes | No

5.20 If "yes" to 5.19, were you worried that if you became less ill the grant would be stopped?

Yes | No

5.21 If "yes" to 5.20, do you feel this contributed to you stopping taking your ART?

Strongly disagree | Disagree | Agree | Strongly agree | N/A

5.22 How much is your monthly income?

R_____

5.23 How much is the monthly income for your household?

R_____ Not Known

5.24 Did having to take ART every day feel like an unpleasant reminder of your HIV status?

Yes | No

5.25 Do you believe that HIV could be cured by traditional medicine or religious practice?

Yes | No

5.26 Were you ever targeted by criminals who were after your antiretroviral treatment?

Yes | No

Depression Screening (PHQ-9):

Over the last 2 weeks how often have you been bothered by the following problems?

6.1 Little interest or pleasure in doing things?

Not at all | Several days | more than half the days | nearly every day

6.2 Feeling down, depressed or hopeless

Not at all | Several days | more than half the days | nearly every day

6.3 Trouble falling asleep, staying asleep or sleeping too much

Not at all | Several days | more than half the days | nearly every day

6.4 Feeling tired or having little energy

Not at all | Several days | more than half the days | nearly every day

6.5 Poor appetite or overeating

Not at all	Several days	more than half the days	nearly every day

6.6Feeling bad about yourself or that you're a failure or have let yourself or your family down

Not at all	Several days	more than half the days	nearly every day

6.7 Trouble concentrating on things, such as reading the newspaper or watching TV

Not at all	Several days	more than half the days	nearly every day

6.8 Moving or speaking so slowly that other people could have noticed. Or being so fidgety or restless that you have been moving around a lot more than usual

Not at all	Several days	more than half the days	nearly every day

6.9 Thoughts that you would be better off dead or of hurting yourself in some way

Not at all	Several days	more than half the days	nearly every day

Other:

7 Are there any other factors you feel contributed to you stopping to take your ART that were not already asked about? If yes please elaborate?

_____

_____

_____

_____

Appendix G: Instructions to authors of the South African Medical Journal (SAMJ)

Author Guidelines SAMJ

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.

Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.

Mask self-citations by referring to your own work in third person.

General article format/layout

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

General:

Manuscripts must be written in UK English.

The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).

Please make your article concise, even if it is below the word limit.

Qualifications, *full* affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.

Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state ‘none’.

Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).

Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.

Please be sure to insert proper symbols e.g. µ not u for micro, a not a for alpha, b not B for beta, etc.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.

Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'

Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

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

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

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

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

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

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

Human Gene Mapping Workshop (HGMW): genetic notations and symbols

HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature

OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions

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

Preparation notes by article type: Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an

important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text.

Structured abstract

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

Background: why the study is being done and how it relates to other published work.

Objectives: what the study intends to find out

Methods: must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.

Results: first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.

Conclusion: must be supported by the data, include recommendations for further study/actions.

Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.

Do not include any references in the abstracts.

Main article

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

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

Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed

Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.

Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.

Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc) that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.

Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.

Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

Start with description of the population and sample. Include key characteristics of comparison groups.

Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.

Do not replicate data in tables and in text.

If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:

E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).

Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

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

Statement of principal findings

Strengths and weaknesses of the study

Contribution to the body of knowledge

Strengths and weaknesses in relation to other studies

The meaning of the study – e.g. what this study means to clinicians and policymakers

Unanswered questions and recommendations for future research

Conclusions

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

Appendix H: Similarity report from the Turnitin application

Reasons Cited for the Interruption of Anti-Retroviral Treatment in the Bloemfontein/Mangaung Area

by Ross Du Plessis

Submission date: 30-Nov-2020 11:58AM (UTC+0200)
Submission ID: 1460108144
File name: MMed_TR_du_Plessis_2007019330_B.docx (869.64K)
Word count: 15844
Character count: 87074

Reasons Cited for the Interruption of Anti-Retroviral Treatment in the Bloemfontein/Mangaung Area

ORIGINALITY REPORT

15%	15%	6%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	hdl.handle.net Internet Source	9%
2	Pamela Anne Nelson, Susie M. Adams. "Primary Cares' Role in Suicide Prevention during the COVID-19 Pandemic", The Journal for Nurse Practitioners, 2020 Publication	2%
3	scholar.ufs.ac.za Internet Source	<1%
4	scholar.ufs.ac.za:8080 Internet Source	<1%
5	www.proefschriftenverpleegkunde.nl Internet Source	<1%
6	ri.ues.edu.sv Internet Source	<1%
7	H Brits, L Branders, M Claassen, D Saaiman, R Strauss, A van Staden, G Joubert. "The prevalence of multiple losses experienced by	<1%

	children from birth to 18 years in the National District Hospital in Bloemfontein", South African Family Practice, 2015 Publication	
8	www.ncwit.org Internet Source	<1%
9	www.ncbi.nlm.nih.gov Internet Source	<1%
10	hhh.gavilan.edu Internet Source	<1%
11	healthnewsreport.blogspot.com Internet Source	<1%
12	Mpoe Johannah Keikelame, Colleen K Murphy, Karin E Ringheim, Sara Woldehanna. "Perceptions of HIV/AIDS leaders about faith-based organisations' influence on HIV/AIDS stigma in South Africa", African Journal of AIDS Research, 2010 Publication	<1%
13	www.ufs.ac.za Internet Source	<1%
14	doras.dcu.ie Internet Source	<1%
15	activeparenting.com Internet Source	<1%

16	eprints.whiterose.ac.uk Internet Source	<1%
17	repository.out.ac.tz Internet Source	<1%
18	wellcomeopenresearch.org Internet Source	<1%
19	"Immunology of Aging", Springer Science and Business Media LLC, 2014 Publication	<1%
20	Adriana A. Beylefeld, Kali D. Nena, Engela A.M. Prinsloo. "Influence of community experiences on first-year medical students' reflective writing", Medical Teacher, 2009 Publication	<1%
21	annals.org Internet Source	<1%
22	Rachel Vreeman, Scanlon. "Current strategies for improving access and adherence to antiretroviral therapies in resource-limited settings", HIV/AIDS - Research and Palliative Care, 2013 Publication	<1%
23	www.cureus.com Internet Source	<1%
24	tbinternet.ohchr.org	

	Internet Source	<1%
25	www.mariannhillmedia.org Internet Source	<1%
26	fairfieldmha.org Internet Source	<1%
27	Siew Chin Ong, Annushiah Vasan Thakumar, Guat See Ooi, Asrul Akmal Shafie, Mohamed Azmi Ahmad Hassali. "Perspectives of the public on the consumption of unregistered health products in Malaysia", International Journal of Pharmacy Practice, 2020 Publication	<1%
28	repository.up.ac.za Internet Source	<1%
29	"HCI International 2020 – Late Breaking Papers: Cognition, Learning and Games", Springer Science and Business Media LLC, 2020 Publication	<1%
30	scholar.sun.ac.za Internet Source	<1%
31	www.termedia.pl Internet Source	<1%
32	journals.plos.org Internet Source	<1%

33	phcfm.org Internet Source	<1%
34	www.mdpi.com Internet Source	<1%
35	creativecommons.org Internet Source	<1%
36	Batya Elul, Paulin Basinga, Harriet Nuwagaba-Biribonwoha, Suzue Saito et al. "High Levels of Adherence and Viral Suppression in a Nationally Representative Sample of HIV-Infected Adults on Antiretroviral Therapy for 6, 12 and 18 Months in Rwanda", PLoS ONE, 2013 Publication	<1%
37	www.cdc.gov Internet Source	<1%
38	www.scribd.com Internet Source	<1%
39	Michael Nicoll. "Satisfaction with respite care: a pilot study", Health and Social Care in the Community, 11/2002 Publication	<1%
40	Rusi Jaspal. "Trans Women and HIV", Springer Science and Business Media LLC, 2020 Publication	<1%
41	www.tandfonline.com Internet Source	

		<1%
42	Bereket Beyene Gebre. "FACTORS ASSOCIATED WITH ALCOHOL USE DISORDER AMONG PEOPLE LIVING WITH HIV/AIDS ATTENDING ART CLINIC, MIZAN TEP UNIVERISTY TEACHING HOSPITAL, SOUTH WEST ETHIOPIA", Research Square, 2019 Publication	<1%
43	Rebecca F. Baggaley. "Human Immunodeficiency Virus: Resistance to Antiretroviral Drugs in Developing Countries", Antimicrobial Resistance in Developing Countries, 2009 Publication	<1%
44	www.science.gov Internet Source	<1%
45	en.wikipedia.org Internet Source	<1%
46	media.proquest.com Internet Source	<1%
47	Rasmussen, Dlama N, David da Silva Té, Lotte Rodkjaer, Inés Oliveira, Candida Medina, Toke Barfod, Alex L Laursen, Peter Aaby, Morten Sodemann, and Christian Wejse. "Barriers and	<1%

facilitators to antiretroviral therapy adherence among patients with HIV in Bissau, Guinea-Bissau: A qualitative study", African Journal of AIDS Research, 2013.
Publication

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		