

Comparing the outcomes of nurse initiated management of antiretroviral therapy in

Tuberculosis - Human immunodeficiency

Virus (HIV) co-infected patients

Vs

HIV mono-infected patients.

Discipline of Public Health Medicine

School of Nursing and Public Health

University of KwaZulu–Natal

South Africa

This research dissertation was submitted in partial fulfilment of the requirement for the Master
of Public Health

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Purpose of the dissertation

This research dissertation was submitted in partial fulfilment of the requirement for the Master of Public Health with the Discipline of Public Health Medicine, School of Nursing and Public Health at University of KwaZulu-Natal. The research component comprises 50% of the degree and is submitted in the journal article manuscript format. The dissertation is to be submitted on 14 December 2016.

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494/15[Sub-study of E248/05]

Declaration

I Niraksha Jithoo declare that

- I. The research reported in this dissertation, except where otherwise indicated, and is my original research.
- II. The work described in this thesis has not been submitted to UKZN or any other tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party. This dissertation has not been submitted for any degree or examination at any other university.

Where a colleague has indeed prepared a thesis based on related work essentially derived from the same project, this must be stated here, accompanied by the name, the degree for which submitted, the University, the year submitted (or in preparation) and a concise description of the work covered by that thesis such that the examiner can be assured that a single body of work is not being used to justify more than one degree.

- III. My contribution to the project was as follows:

The study was done retrospectively from CAPRISA AIDS treatment data base. My role involved writing and submitting the protocol ,obtaining ethics approval, drawing up the analysis required , analysing data with the statistician, doing the write up for the dissertation as well as the journal article. I will also submit the article to journal of public health.

- IV. The contributions of others to the project were as follows:

My supervisor and co-supervisor were actively involved in reviewing the dissertation and providing guidance.

Nonhlanhla Yende, statistician who assisted with the analysis.

- V. This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

- VI. This dissertation does not contain other persons' writing, unless specifically acknowledged as being sourced from other researchers. Where other written sources have been quoted, then:
1. a) their words have been re-written but the general information attributed to them has been referenced;
 2. b) where their exact words have been used, their writing has been placed inside quotation marks, and referenced.
- VII. Where I have reproduced a journal publication of which I am an author, I have indicated in detail which part of the publication was actually written by me alone and not by other authors, editors or others.
- VIII. This dissertation does not contain text, graphics or tables copied and pasted from the Internet, unless specifically acknowledged, and the source being detailed in the dissertation and in the References sections.

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Table of contents

Content

| | |
|--|-----|
| Purpose of the dissertation | iii |
| Declaration..... | iv |
| Acknowledgement | vi |
| Table of contents..... | vii |
| Table of Figures | x |
| Table of Tables | x |
| Acronyms and Abbreviations | xi |
| Chapter 1..... | 1 |
| 1. Introduction..... | 1 |
| ■ Background..... | 1 |
| ■ Purpose of the study..... | 2 |
| ■ Research Hypothesis:..... | 2 |
| ■ Specific Objectives | 2 |
| ■ Type of research..... | 3 |
| ■ Definitions | 3 |
| ■ Organisation of the dissertation | 3 |
| Chapter 2..... | 5 |
| 2 Literature Review..... | 5 |
| ■ The World Health Organisation strategy | 5 |

| | | |
|------------------------------|---|----|
| ■ | Task shifting | 6 |
| ■ | National Strategic Plan and NIMART | 8 |
| ■ | Department of Health (DOH) ART guidelines | 9 |
| ■ | Evidence on NIMART | 10 |
| ■ | Sustainability of NIMART | 11 |
| ■ | Summary of literature review | 12 |
| Chapter 3..... | | 14 |
| 3 | Journal article manuscript..... | 14 |
| ■ | Author requirements | 14 |
| ■ | Article for submission to journal | 16 |
| <i>Abstract</i> | | 18 |
| <i>Objectives</i> | | 18 |
| <i>Study design</i> | | 18 |
| <i>Method</i> | | 18 |
| <i>Results</i> | | 18 |
| <i>Conclusion</i> | | 19 |
| <i>Key words</i> | | 19 |
| Introduction | | 19 |
| Method | | 21 |
| Results | | 22 |
| Discussion | | 30 |
| Conclusion | | 32 |
| Acknowledgement | | 32 |

| | |
|---|----|
| Funding | 32 |
| References | 33 |
| Chapter 4..... | 35 |
| 4 Synthesis, limitations, conclusion and recommendations..... | 35 |
| ■ Additional data for discussion | 35 |
| ■ Limitations | 37 |
| ■ Recommendations..... | 39 |
| ■ Conclusion | 40 |
| ■ Summary | 41 |
| 5 References..... | 42 |
| 6 Annexures | 45 |
| ■ Protocol..... | 45 |
| ■ Ethic approval..... | 73 |
| ■ Gatekeeper Permission..... | 75 |
| ■ Journal of Public Health author guideline..... | 77 |

Table of Figures

Figure 1: Kaplan-Meier curve for probability of death for HIV-TB co-infected and HIV mono-infected PLWHA at month 6, 12, 18 and 24..... 26

Table of Tables

Table 1: Baseline characteristics of TB-HIV co-infected and HIV mono-infected group **Error! Bookmark not defined.**

Table 2: Mortality rate (MR) for TB-HIV co-infected and HIV mono-infected at 6, 12, 18 and 24 months of study follow-up **Error! Bookmark not defined.**

Table 3: Multivariate analysis of the predictors of mortality for the study . **Error! Bookmark not defined.**

Table 4: The most common adverse events seen in study by either doctor or nurse, including referral to clinician for both TB-HIV co-infected and HIV mono-infected group. **Error! Bookmark not defined.**

Table 5: Reasons for termination of TB-HIV co-infected and HIV mono-infected from the study 36

Acronyms and Abbreviations

| | |
|---------|---|
| AE | Adverse Events |
| AIDS | Acquired Immune Deficiency Syndrome |
| ART | Antiretroviral Therapy |
| BMI | Body Mass Index |
| CAPRISA | Centre for Aids Prevention Research in South Africa |
| CAT | CAPRISA Aids Treatment |
| CNS | Central Nervous System |
| CRF | Case Report Form |
| CVS | Cardiovascular System |
| DDI | Didanosine |
| DOH | Department of Health |
| EFV | Efavirenz |
| ENT | Ear, Nose and Throat |
| GIT | Gastrointestinal |
| GUT | Genitourinary |
| HIV | Human Immunodeficiency Virus |
| IRIS | Immune Reconstitution Inflammatory Syndrome |
| KZN | KwaZulu-Natal |

| | |
|--------|--|
| LRTI | Lower Respiratory Tract Infection |
| MR | Mortality Rate |
| NIMART | Nurse Initiated Management of Antiretroviral Therapy |
| NGO | Non-Government Organisation |
| PLWHA | People Living with HIV and AIDS |
| PPE | Papular Pruritic Eruption |
| RCT | Randomized Control Trial |
| SA | South Africa |
| TAC | Treatment Action Campaign |
| TB | Tuberculosis |
| 3TC | Lamivudine |
| TDF | Tenofovir |
| μL | Microliter |
| URTI | Upper Respiratory Tract Infection |
| VL | Viral Load |
| WHO | World Health Organisation |

Chapter 1

1. Introduction

In the introductory chapter I will outline the concept of access to universal care and the role of nurses in implementing and managing antiretroviral treatment. I will proceed to discuss the purpose of the study with a focus on my hypothesis, specific objectives, type of research and finally the organisation of the dissertation.

Globally in 2015 there were 36.7 million people living with HIV (PLWHA), of which 25.6 million were in sub-Saharan Africa and approximately seven million in South Africa (SA).^{1, 24} Since the discovery of Human Immunodeficiency Virus (HIV) in 1981 “tens of millions of people” have died from Acquired Immune Deficiency Syndrome (AIDS).²

The World Health Organisation (WHO) in its efforts to reduce mortality introduced the concept of universal access to treatment for HIV by 2015, which also encompasses Millennium Development Goal 6.³ This goal focused on combating HIV, AIDS, malaria and other diseases.³

Background

Primary health care nurses provide health care to thousands of patients both in rural and urban regions of SA and are a valuable resource for providing education, support and care for communities.^{4, 5} These nursing practitioners often work under circumstances where access to a medical doctor is a scarce commodity so they have to utilize their experience, skill and knowledge to provide good quality service to patients.^{4, 5}

In September 2010 the South African government initiated a policy that allowed for the provision of antiretroviral medication by primary health care nurses to people living with HIV and AIDS (PLWHA).^{4, 5} There are many challenges and lessons that can be learned from an established nurse-based rollout programme for ART. These programmes have been rolled out in

an effort to meet the demand of providing treatment to PLWHA and have shown to be successful in resource constrained settings. ^{3, 4,5,17}

In a setting like SA this study could provide valuable information on gaps or areas of weakness that currently exist in the system.

██████████ *Purpose of the study*

The purpose of this study was to compare the outcomes of nurse initiated management of antiretroviral therapy (NIMART) in TB-HIV co-infected patients vs HIV mono-infected patients in an urban non-government organisation(NGO) funded clinic in KwaZulu-Natal (KZN), between January 2010-December 2012.

██████████ *Research Hypothesis:*

NIMART management of TB-HIV co-infected patients requires complex clinical care, and is associated with worse outcomes as compared to HIV mono-infected patients.

██████████ *Specific Objectives*

The specific objectives of this study were designed to include a descriptive profile within a NIMART programme as well as an analysis of the differences between the two cohorts. The descriptive profile involved describing and comparing the patient demographic variables and the HIV and AIDS disease profile in TB-HIV co- infected patient's vs HIV mono- infected patients.

The difference between TB-HIV co-infected and HIV mono-infected patients will be analysed in terms of :

- Reasons for referrals of NIMART patients to the medical officer;

- Clinical outcomes; and
- Mortality.

█ *Type of research*

This was a health system research with a population based epidemiological component.

█ *Definitions*

The definitions listed below indicate specific definitions and how these would apply to the study.

- HIV WHO Staging: The WHO classification of HIV for adults and adolescents was used for the purpose of this study. We will consider this in the present document, the category of adults and adolescents aged 15 years and over for surveillance purposes. ¹⁶
- Urban: Relating to characteristic of, or constituting a city. For the purpose of the study the word urban refers to the setting in the city of Durban.

█ *Organisation of the dissertation*

This dissertation is presented in the Journal Article Manuscript Format approved by the University of KwaZulu-Natal. In place of presenting a 'Results' chapter, a Journal Article Manuscript, ready for submission to Journal of Public Health for peer review is presented.

The organisation of the chapters is discussed below.

Chapter 1 focuses on a brief introduction, background, purpose of the study, the hypothesis, the objectives, type of research and definitions used.

Chapter 2 comprises a detailed literature review and focuses on current literature available.

Chapter 3 comprises the journal article ready for submission to Journal of Public Health.

Chapter 4 presents the synthesis of the study which is a review of the additional results that are not included in the journal article, the limitations of the study, possible bias as well as the conclusions and overall recommendations of the study. The references and annexures follow Chapter 4.

Chapter 2

2 Literature Review

The following section describes the background to the NIMART strategy, highlighting the need to overcome clinical staff shortages and initiatives to achieve the Millennium Development Goals with regard to HIV rollout. The clinical trial summaries reflect the outcomes of various NIMART programme and task shifting. Data was obtained by means of searches conducted on Google, Google scholar, PubMed and Cochrane data base review. Search terms used were 'NIMART', 'task shifting', 'WHO', 'Millennium Development Goals', nurses' views on NIMART, health workforce and TB-HIV treatment.

■ *The World Health Organisation strategy*

In 2006 the World Health Organisation declared the sub-Saharan region of Africa to be in crisis because it had less than the minimum WHO recommendation of 2.3 doctors and nurses per 1 000 patient population.⁵ This shortage of doctors led to idea of decentralizing ART services to nurse-led clinics which would improve patient access to HIV management and treatment.⁵

In 2008 the burden of HIV was expanding globally and the lack of highly trained personnel to administer the treatment lead the WHO to provide a global recommendation document of task shifting.⁶ The document referred to shifting specific NIMART management tasks from doctors to nurses. Included in the tasks affected by this is determining the eligibility of patients for treatment, determining which line of therapy needs to be commenced, management of the side effects of treatment and the clinical monitoring of the patients.⁵

The document was proposed with the aim of overcoming the shortages of staff, providing increased access to ART and meeting the Millennium Development Goals.^{6,8} The sub-Saharan region was most affected by the HIV epidemic and task shifting would therefore prove to be beneficial here.⁷

Task shifting

Task shifting involves the transference of certain tasks which were previously performed by highly skilled personnel such as doctors to less skilled personnel such as nurses.⁶ Studies have shown that task shifting allows better access to HIV services with a result of greater efficiency of service delivery.⁸ For example, the number of HIV treatment initiations doubled in Malawi due to task shifting.⁷ In Uganda task shifting resulted in an increase in enrolment of patients on to the ART programme by 20%.⁷ In Botswana the implementation of NIMART saw nearly 20 000 patients receiving ART in rural areas by December 2007.¹⁷

A systematic review conducted by Callaghan *et al.* on 84 articles on task shifting for HIV care and treatment revealed that task shifting is cost effective and can offer good quality care to more patients than a doctor-based approach.¹⁷ There are many facets involved in the costs of running a clinic for ART of which salaries are the largest component.¹⁷ In a study carried out in South Africa the cost of the doctors' salaries was estimated to be 42 percent of the total clinic cost.¹⁷ Task shifting reduced dependence on doctors which could lead to a reduction in ART clinic costs.¹⁷ This could have equated to more surplus money to keep the clinic running, better facilities or an increase in the patient number that were receiving ART. The review also revealed that task shifting led to time saving.¹⁷ This was based on the assumption that the time saved allowed senior staff to focus on the management of complicated patients and a decrease in clinic waiting time with an ultimate reduction in loss to follow ups.¹⁷ A study in Rwanda that analysed time saving in NIMART clinics revealed that task shifting would result in 183 percent increase in doctor capacity for tasks that are non-HIV related.¹⁷ In their study Emdin *et al.* found that task shifting contributed to better patient compliance and reduced loss to follow up. They attributed this to the fact that access to treatment was closer to the patient's home and time off work and travel costs were reduced.⁷

In 2006 a decentralized approach of ART from hospital to primary health care clinics was adopted in rural Lusikisiki in South Africa to mitigate the effects of staff shortages.¹⁹ This model resulted in rapid initiation of ART and better treatment retention of follow up patients (2 percent

vs 19 percent loss to follow-up).¹⁹ In addition, there was 95 percent coverage of people receiving ART in 2006 under this model of care.¹⁹

The outcomes of task shifting in the sub-Saharan region have yielded positive clinical outcomes.¹⁷ Uganda showed good clinical outcomes just 2 years into their NIMART programme. Rwanda, Lesotho and South Africa have also reported good clinical outcomes as well as retention on ART.¹⁷

The impact of task shifting and ultimately ART scale up was also examined from a provider's perspective in a health care worker survey that took place in 2 South African provinces (KwaZulu-Natal and Western Cape) in 2006.²⁰ The survey was completed by 269 health care professionals and showed that ART scale up with nurses was not perceived to impose an additional burden in the health system. On the contrary, greater levels of job satisfaction was present.²⁰ One possible explanation is that as a result of being responsible for providing lifesaving medication, the nurses viewed themselves as a critical component in the treatment paradigm of HIV patients.²⁰ This ultimately boosted the morale of the healthcare personnel.²⁰ Work benefits like remuneration also led to job satisfaction. The study also revealed that workers in the ART clinics reported a lighter workload with higher level of staffing and lower sick leave rates.²⁰

The task shifting model did not only apply to nurses for ART management but also other community health workers.¹⁷ The sub-Saharan region went further than task shifting within a clinical environment to the introduction of community-based services that were outside the clinic setting.¹⁷ The results from a trial in Uganda which compared home-based care through lay providers with facility-based care in ART found that the rates for viral load suppression, failure and mortality were similar.¹⁷ Compliance with ART is imperative for a patient to achieve viral load suppression and overall survival. Two studies in Malawi which introduced community based lay providers as a support to facility based ART treatment revealed different results.¹⁷ One study showed better survival and retention rates on ART compared with patients who did not receive this support.¹⁷ However, another Malawian study showed contrary results where community health care workers were not able to identify eligible patients for ART as efficiently

as doctors' could.¹⁷ These results reveal that task shifting is beneficial but also needs to be closely monitored to establish loop holes in the system and then provide guidance and training to ensure successful outcomes.

Ongoing education and training of staff on ART practices has been identified as a means to overcome the challenges faced in task shifting.¹⁷ This was demonstrated in a study done in South Africa on community health care workers.¹⁷ Similarly in Zambia 85 percent of lay counsellors identified extra training on ART as a means to improve service delivery.¹⁷ A descriptive analysis of the 1 479 HIV-TB queries received from nurses in 2012 at the "South African national HIV and TB health care worker hotline" identified NIMART, drug side effects and laboratory result interpretation as the most common queries received.¹⁸

Zachariah et al proposed the following in their paper on task shifting in sub-Saharan Africa.²¹ The scale up of ART services to provide lifesaving treatment to many more people was seen as a better option than a doctor-based facility in terms of sustainability and cost effectiveness.²¹ They proposed some of the challenges that should be addressed to sustain such a model is maintaining the quality of health care, staff satisfaction and motivation and preventing staff deaths from HIV itself.²¹ The task shifting concept was introduced in South Africa in 2010.⁹

■ *National Strategic Plan and NIMART*

South Africa has a quadruple burden of disease which comprises communicable diseases such as HIV, AIDS and TB, maternal and child morbidity and mortality, non-communicable disease and violence, injuries and trauma.⁹

In 2000 in order to combat the problem of poor health, poverty, hunger, inequalities in gender and lack of basic services such as clean water the United Nations adopted a UN Millennium declaration of which 189 countries adopted.²¹ This declaration led to development of eight Millennium development goals that were pledged to be achieved by 2015.²¹

In line with the Millennium Development Goal 6 (combating HIV, AIDS, malaria and other diseases), and to address the SA burden of disease, the National Strategic Plan 2009-2014 for Health was developed.^{3,9} One of the imperatives was to speed up the implementation of

HIV / AIDS and Sexually Transmitted Infections National Strategic Plan from 2007-2011 with an increased focus on TB and other communicable diseases.⁹

An analysis of South Africa's challenges brought on the realisation that HIV was a major contributor to morbidity and mortality and action needed to be taken to improve this outcome.⁹ Thus the government rolled out the NIMART programme in 2010.⁹ From 2010 to 2013 the number of people who were initiated on HIV treatment increased from 923 000 to 1.9 million.⁹ The goal in South Africa is to ultimately achieve an HIV and AIDS free generation under the age of 20 by 2030 as stipulated in National Development Plan.⁹

Department of Health (DOH) ART guidelines

In South Africa the decade of HIV denialism was opposed by the actions of the Treatment Action Campaign (TAC) who exerted pressure on the existing South African government to provide treatment and care for PLWHA.¹⁰ In 2010 ART was provided to all PLWHA that had a CD4 count of 200 cells per microliter (μL) or less, with the exclusion of TB co-infected and pregnant females who were initiated on treatment with higher CD4 count of 350 cell/ μL .¹⁰

By 2011 the guidelines were updated for ART initiation to include all PLWHA to start at CD4 counts of 350 cells/ μL or less.¹⁰ By 2013 the guidelines were updated once again to initiate treatment with antiretroviral drugs irrespective of their CD4 for PLWHA co- infected with TB and all pregnant women.¹⁰ The massive shift in initiating ART at an earlier CD4 count meant a scale up of HIV treatment programmes that required trained personal.¹⁴ The SA government has introduced an update to the guideline for ART initiation in 2016 by advocating that all PLWHA start ART irrespective of their CD4 count.²³ The availability of trained personnel is more imperative as we gearing for the largest programme for ART initiation in SA.

Evidence on NIMART

The Streamlining Tasks and Roles to Expand Treatment and Care for HIV (STRETCH) trial, conducted in South Africa, was a parallel, open label cluster randomised controlled trial (RCT) conducted in 31 public sector clinics in the Free State during the period of 2008 to 2010.¹¹ There was random allocation of the different clinics into an intervention arm (16 clinics) and a control arm (15 clinics).¹¹ Patients were assigned to either cohort 1 which consisted of adult patients waiting to start ART, or cohort 2 which consisted of patients had already been on ART for at least six months.¹¹

Cohort 1 inclusion criteria were a CD4 count of ≤ 350 cells per μL , making them eligible for ART. These patients were monitored for a year following enrolment.¹¹ Failure of patients to return to the clinic following enrolment resulted in them being excluded from the study.¹¹ Informed consent was received from clinic staff and not from the patients as the trial was studying a managerial procedure.¹¹ However the patients were informed of the study and its interventions.¹¹ The control arm of the trial employed the current standard of care in the South African public health sector for HIV/AIDS treatment. Patients that tested positive with the HIV virus were seen by nurses to determine their eligibility for treatment which was a CD4 count < 200 cells per μL , WHO Stage 4 condition or were pregnant with a CD4 count < 350 cells per μL .¹¹ These patients were seen by a doctor who initiated treatment.¹¹ The follow-up visits could be done in rural clinics near the patient's home by nurses who received the medication from hospital pharmacy for dispensing.¹¹

The clinics which had been randomly selected to the intervention arm had employed the protocol for the STRETCH trial. Nurses were allowed to initiate and prescribe ART for the eligible patients.¹¹ The nurses had been provided with a minimum of four ART training sessions on the prescription of ART, the treatment algorithm, the management and monitoring of side effects of the medication and when to refer the patient to a doctor.¹¹ Data was initially collected on paper and then transferred to an electronic data base.¹¹

The two cohorts differed in terms of primary outcomes. Cohort one had an outcome of time to death and cohort two was undetectable viral loads 12 months after enrolment.¹¹ The undetected

viral load was defined as a viral load < 400 copies per ml. ¹¹ Cohort one had 9252 participants and cohort two had 6231 participants. ¹¹

The results showed that patients in cohort one had a 47% less chance of death if they were on ART than those who were not on ART, and the study was able to attain the goal of viral load suppression in patients on treatment. ¹¹ There was no single outcome that was worse in the intervention group as compared to the control group. This trial demonstrated that task shifting is possible and that ART initiation and follow up can be done safely by nurses. ¹¹

Problems identified in the trial included nurses' reluctance to initiate treatment when there was a doctor available in the clinic. The poor delivery of ART to clinics resulted in the additional problem of lack of treatment available in clinics. This hampered the nurses' ability to adequately start ART. ¹¹

The evidence for NIMART is further highlighted by another RCT that was conducted by Sanne *et al.* in South Africa. ¹² The trial looked at doctor versus nurse management of HIV infected persons in primary health care clinics and was powered for non-inferiority. ¹² There was an intervention arm and control arm to the trial. ¹² There were 404 patients randomly selected for the intervention arm and 408 patients for the control arm of the trial. ¹² The inclusion criteria were adult patients that had been on ART for less than six weeks. ¹² The follow up period of the patients was 120 weeks. ¹² Study end points were mortality, virological failure, loss to follow ups, toxicity failure, defaulting visits between the nurse- and doctor-managed groups. ¹² The study concluded that no significant difference was found between these end points. ¹²

█ Sustainability of NIMART

The success of NIMART has been proven in both the public sector as well as in non-government organisations (NGO'S) with private funding. A study conducted between 2004 and 2010 by Naranbhai *et al.* in a rural HIV clinic in KZN, showed that task shifting was able to positively influence long term treatment outcomes. ¹³ The nurses were not involved in ART initiation,

rather in the follow up of treatment initiated patients.¹³ There was an onsite doctor for ART initiation and for the management of complications.¹³ The results showed that virological suppression was achieved in approximately 90% of patients during the study period of 60 months.¹³

The success of NIMART has been well demonstrated in the literature. However, the barriers to NIMART also need to be addressed. The Foundation of Professional Development (FPD) conducted a study in seven provinces in SA between October 2010 and March 2011 which looked at the number of nurses that were implementing NIMART within two months of patient's attending the clinic. The endpoints were quality of care and barriers to NIMART implementation.¹⁵ The results indicated that only 72% of nurses initiated treatment.¹⁵ The barriers to initiation of treatment identified in this study were a lack of mentorship; lack of training in pharmacology; lack of clinical skills and shortage of primary health care nurses.¹⁵ A cross-sectional quality of care study in Khayelitsha in 2011 to 2012 showed that a clinical mentorship programme improved clinical skills of nurses and boosted their confidence in initiating patients on to ART.¹⁴ The challenges highlighted within the above trials provides an insight into the operational challenges which have to be overcome in the implementation of these programmes in South Africa.

Summary of literature review

Task shifting has been adapted and has been shown to be effective and sustainable personnel strategy in the treatment of HIV patients. NIMART implementation has been introduced

In SA, however, some barriers still exist with regards to operational challenges within the existing system. Most of the literature available addresses success of task shifting and NIMART with regards to numbers' initiated, clinical outcomes, mortality, adherence, cost effectiveness, and challenges encountered by nurses.

Tuberculosis is one the most common infection seen in PLWHA and is the major cause of death in PLWHA. ^{19, 22} The identification of both pulmonary, smear negative and extra pulmonary TB is critical in providing improved clinical outcomes in PLWHA. ²² There is a gap in data available on referrals of adverse events to medical officers especially in TB-HIV co-infected patients.

This paper aims to look at complexities and challenges associated with TB-HIV co-infection by focusing on clinical outcomes, mortality and adverse events seen and referred to medical officers as compared to HIV mono –infection.

Chapter 3

3 Journal article manuscript

In this chapter I am presenting a Journal Article Manuscript which describes the new research that I completed as part of my Master of Public Health degree at the University of KwaZulu-Natal. I have prepared the article to be submitted to the Journal of Public Health. The guide for author submission for the Journal of Public Health is attached as annexure 6.4. This guide determined the format, layout and word count of the article, which might be different to rest of the dissertation.

The type of article is an original research article and should be 3000 words. Although this article has not yet been published it is ready to be sent off to the editors for peer review. I have included the Tables and Figures where I think they could be included in the final published article – as opposed to being submitted separately as required by the editors.

There are some additional results, discussion and limitations which were not included in the article in Chapter 4 of this dissertation.

Author requirements

Below I have summarized briefly the author requirement for the article.

1. The article should be maximum of 3000 words.
2. Title page should have all authors, their main degrees (max of two), name and location of institution where study was done and contact details.
3. The structure the abstract should have the following headings:
 - Objectives
 - Study design
 - Method
 - Result
 - Conclusion
 - Key words

4. The headings following the abstract are :
 - Introduction
 - Methods
 - Results
 - Discussion
 - Acknowledgements, declarations and ethics approval
 - References.
5. The tables and figures should be kept at minimum

The rest of the guideline for authors can be found in annexure 6.4.

Article for submission to journal

Comparing the outcomes of nurse initiated management of antiretroviral therapy in Tuberculosis-HIV co-infected patients and HIV mono-infected people living with HIV and AIDS in South Africa.

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Abstract

Objectives

Managing HIV associated Tuberculosis in people living with HIV and AIDS (PLWHA) requires complex clinical care, is associated with adverse clinical outcomes and warrants referral to medical officers as compared to those that are HIV mono-infected.

The objectives of this study are to compare the clinical outcomes, mortality and reasons for referral in two groups of PLWHA, with Tuberculosis associated with HIV (TB-HIV) and HIV mono-infection. The study was performed in a non-governmental funded, nurse initiated management of antiretroviral (NIMART) programme in a province of South Africa from January 2010 to December 2012.

Study design

An observational, retrospective, analytic cohort study design was used.

Method

Both groups of PLWHA were commenced on a once daily ART regimen and enrolled into the NIMART programme by two professional nurses with an onsite medical officer to attend to complex cases. The two groups were classified for TB at baseline based on active TB infection and not latent TB infection. Data was collated from case report forms stored on a special electronic data base and was processed and analysed using appropriate biostatistics.

Results

A total of 1096 PLWHA that were HIV mono-infected 622 (57%) and 474 (43%) TB-HIV co-infected were enrolled and followed up for 18 to 24 months. The two groups were significantly different in terms of gender, body mass index, viral load and disease staging at baseline. Both groups maintained a sustained CD4 count increase and viral load suppression during the period of the programme. There were 35 deaths in the TB-HIV co-infected group with a mortality rate (MR) 7.4 per 100 person years [95% Confidence Interval (CI): 5.1 - 10.3] and 38 deaths in the

HIV mono-infected group with a MR of 7.8 per 100 person years at 24 months (95% CI: 5.5 - 10.7). These mortality rates were not significantly different. Multivariate analysis on predictors of mortality for all PLWHA revealed that the risk of mortality was increased if there was a CD4<50 cells/mm³ (p=0.003) and WHO stage 4 condition (p>0.001) for both groups. There were a total of 1867 adverse events (968 in the TB-HIV co-infected and 899 in the HIV mono-infected group). There were 963 and 808 doctor referrals from 370 and 338 PLWHA from the TB-HIV co-infected and HIV mono-infected groups respectively. The most common reason for referral for the TB-HIV co-infected group were for peripheral neuropathy (61); rash (41) and TB- Immune Reconstitution Inflammatory Syndrome [IRIS] (40). The most common referrals for the HIV mono-infected group were for peripheral neuropathy (35); papular pruritic eruption (21) and upper respiratory tract infections (20).

Conclusion

Our study showed that the NIMART is effective for PLWHA that are TB-HIV co-infected as it is for mono-infected patients when access to a medical officer for referral is available.

439 words

Key words

Retrospective cohort study

Mortality rate

Task Shifting

Introduction

There were 36 million people living with Human Immune Deficiency Syndrome (HIV) and Acquired Immunodeficiency Syndrome (AIDS) (PLWHA) globally in 2015, with 26 million in sub-Saharan Africa and approximately 7 million in South Africa (SA).^{1, 15} The burden of HIV was expanding globally in 2008 and the lack of highly trained personal to administer the treatment, led the World Health Organisation (WHO) to recommend task shifting, the transference of certain tasks which were performed by highly skilled personal such as doctors to

less skilled personal such as nurses.² Task shifting aims to overcome the shortages of staff and being able to provide increased access to antiretroviral therapy (ART) and meet the Millennium Development Goals.^{2,3}

There was a realisation in SA that HIV infection was a major contributor to morbidity and mortality and as part of the strategy to address the problem NIMART was commenced in 2010.⁴ From 2010 to 2013, the number of people initiated on ART increased from 923 000 to 1.9 million.⁴ The SA government introduced an update to the guideline for ART initiation in 2016 by advocating that all PLWHA start ART irrespective of their CD4 count.¹⁰ The availability of trained health care personnel is essential in order to deliver care for the large number of PLWHA who need ART in SA.

The effectiveness of NIMART was shown in the STRETCH trial “Streamlining Tasks and Roles to Expand Treatment and Care for HIV”, a parallel; cluster randomised controlled trial conducted in 16 public sector clinics in the Free State during the period of 2008 to 2010.⁵

A study done by Naranbhai *et al.* in a rural HIV clinic in the KwaZulu-Natal (KZN) province showed that task shifting in NIMART was able to improve long term treatment outcomes.⁶ Virological suppression was achieved in 89-97% of patients for period of 60 months and there was 82% retention ($p < 0.0001$) up to 24 months.⁶

Tuberculosis is one the most common infections seen in PLWHA and is the major cause of death in PLWHA.^{11,12} The identification of both pulmonary and extra pulmonary TB is critical in providing improved clinical outcomes in PLWHA.²² There is a gap in the data available on referrals of adverse events to medical officers, especially in TB-HIV co-infected patients.

This paper aims to look at complexities and challenges associated with TB-HIV co-infection by focusing on clinical outcomes, mortality and adverse events seen and referred to medical officers as compared to HIV mono –infection in a non-governmental organisation (NGO) funded, nurse initiated management of antiretroviral programme in KZN(a province in SA) from January 2010 to December 2012.

Our study setting was an urban HIV treatment clinic in KZN run by an NGO, Centre for Aids Prevention Research in Southern Africa (CAPRISA). In 2010, in line with the National Health Department's policy, nurses began to initiate ART. The medical officer were employed full time and their role was to be a mentor, review all laboratory results, and attend to patients with treatment regimen failures, hospital admission, and referrals from nurses. The programme had the services of lay counsellors to assist with adherence to treatment and trackers to trace study participants that missed scheduled visits.

Method

An observational, retrospective, analytic cohort study design was used. The study population consisted of naïve adult PLWHA, either with TB-HIV co-infection or HIV mono- infection. The two groups were classified for TB at baseline based on active TB infection and not latent TB infection .The PLWHA were allocated into the respective groups based on their TB status at enrolment into the ART programme. We decided to use a sample size of 1000 which increased the power to 85%, however we finally settled on including all the PLWHA (1096) for the study period as the data was readily available.

For the participants in this study NIMART was initiated in both groups. Detailed records were collected by nurses on a case report form (CRF). Data was quality reviewed by data manager and stored on an electronic data base.

The data was analysed using unpaired t-test, and Wilcoxon rank sum test for continuous data and Fisher's exact test for categorical data to compare demographics and clinical characteristics between the 2 groups. Data was censored at 24 months post ART initiation. Kaplan-Meier was used to construct survival curves and compare them using the log-rank test. Predictors of mortality were assessed through both univariate and multivariate proportional hazards regression. P values less than 0.05 were considered statistically significant. All analyses were conducted using SAS, version 9.4 (SAS Institute INC., Cary).

An adverse event in study was defined as any untoward event that occurred to a participant after starting ART and was graded via the Division of Aids (DAIDS) grading system.

Ethics approval was obtained from the University of KwaZulu-Natal, South Africa Biomedical Research Ethics Committee. BE 494/15 - Sub-study of E248/050. Informed consent was waived by ethics committee.

Results

A total of 1096 PLWHA were enrolled in the two year study. Most (622, 57%) were HIV mono-infected and 474 (43%) were TB-HIV co-infected.

Baseline characteristics

The baseline characteristics analysed for both groups were body mass index (BMI), viral load (VL), World Health Organisation (WHO) disease stage, age, gender and a previous history of TB. The TB-HIV group had significantly lower (BMI) [21.4 (Interquartile Range (IQR): 19.2 - 24.1) compared to the HIV-mono infected group. (23.9 - IQR: 21.0 - 27.7) ($p < 0.001$); a higher mean VL (5.1 vs 4.8, $p < 0.001$); more WHO Stage 4 disease (23.8% vs 11%, $p < 0.001$); and, more males (54% vs 40 %, $p < 0.001$) (Table 1). There was no difference in age and CD4 count between the two groups.

Table 1: Baseline characteristics of TB-HIV co-infected and HIV mono-infected group

| Variable | TB-HIV co-infected (N=474) | % | HIV mono-infected (N=622) | % | p-value |
|---|----------------------------|------------------|---------------------------|------------------|---------|
| Age (years), median(IQR) | 35 | IQR 30 - 41 | 34 | IQR 29-41 | 0.389 |
| Age (years), n (%) | | | | | 0.565 |
| <24 | 15 | 3.2 | 23 | 3.7 | |
| 24-34 | 216 | 45.6 | 300 | 48.2 | |
| 35+ | 243 | 51.3 | 299 | 48.1 | |
| Women | 218 | 46.0 | 373 | 60.0 | <0.001 |
| Men | 256 | 54.0 | 249 | 40.0 | |
| BMI(kg/m ²), median | 21.4 | IQR 19.2-24.1 | 23.9 | IQR 21.0-27.7 | <0.001 |
| CD4 count(cells/mm ³), median | 144 | IQR 72 -228 | 146 | IQR 77 - 210 | 0.512 |
| CD4 count | | | | | 0.482 |
| <50 | 69 | 15.5 | 96 | 16.5 | |
| 50-200 | 231 | 51.8 | 316 | 54.3 | |
| >200 | 146 | 32.7 | 170 | 29.2 | |
| Log VL, mean(SD) | 5.1 | 0.9 | 4.8 | 0.7 | <0.001 |
| WHO Stage 1-3 | 361 | 76.2 | 549 | 89 | <0.001 |
| WHO Stage 4 | 113 | 23.8 | 68 | 11 | |
| Previous history of TB | 120 | 25.8 | 182 | 30.8 | 0.086 |

Clinical outcomes

The clinical outcomes were assessed by looking at the mean CD4 count increase and VL suppression at different time points. The mean CD4 count increase and VL suppression (< 400 copies/ml) were not significantly different between both the groups. At month 12 the mean CD4 count increase in TB-HIV co-infected group [n=302] was 200 cells/mm³ (95% CI: 174-226) and HIV mono infected group [n=215] was 184 cells/mm³ (95% CI: 166-202) p = 0.291). The proportion of PLWHA with a viral load suppression at month 12 in TB-HIV co-infected group

was 93.6% (95% CI: 293-313) and in the HIV mono-infected group was 89.1% (95% CI: 204-229) p=0.644.

Mortality

A key outcome in study was mortality. There were 35 deaths in the TB-HIV co-infected group (MR - 7.4 per 100 person years (95% CI: 5.1 - 10.3) and 38 deaths in the HIV mono-infected group (MR - 7.8 per 100 person years (95% CI: 5.5 - 10.7) at 24 months. Mortality rate among PLWHA who are mono-infected was slightly higher than for those who were co-infected (Table 2). However, these mortality rates were not significantly different. The Kaplan-Meier curve for probability of death also showed no significant differences between the 2 groups (Figure 1).

Table 2: Mortality rate (MR) for TB-HIV co-infected and HIV mono-infected at 6, 12, 18 and 24 months of study follow-up

| Follow-up | TB-HIV co-infected | | | | HIV mono-infected | | | | Rate ratio | 95% CI | p-value |
|-----------------|--------------------|--------------|-----|----------|-------------------|--------------|------|----------|------------|-----------|---------|
| | No of deaths | Person-years | MR | 95% CI | No of deaths | Person-years | MR | 95% CI | | | |
| Month 6 | 18 | 224 | 8.0 | 4.8-12.7 | 28 | 281 | 10.0 | 6.6-14.4 | 0.8 | 0.45-1.46 | 0.485 |
| Month 12 | 32 | 399 | 8.0 | 5.5-11.3 | 37 | 432 | 8.6 | 6.0-11.8 | 0.9 | 0.58-1.49 | 0.764 |
| Month 18 | 34 | 463 | 7.3 | 5.1-10.3 | 38 | 477 | 8.0 | 5.6-10.9 | 0.9 | 0.58-1.46 | 0.724 |
| Month 24 | 35 | 473.38 | 7.4 | 5.1-10.3 | 38 | 485.77 | 7.8 | 5.5-10.7 | 1.0 | 0.6-1.5 | 0.827 |

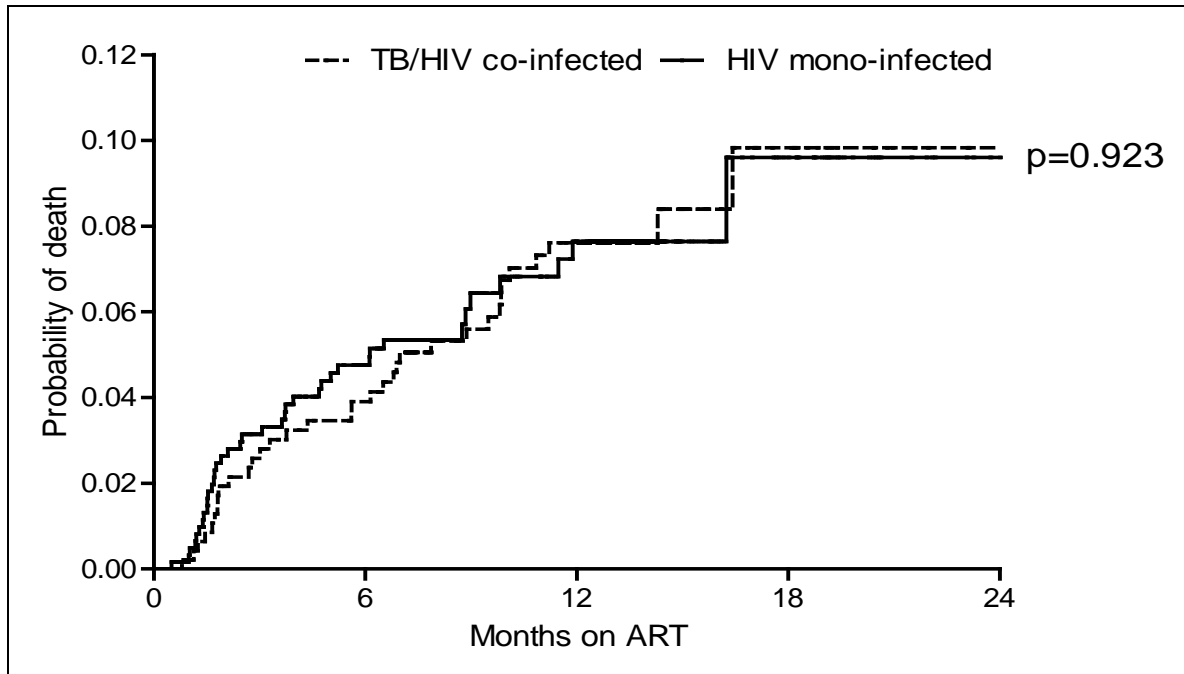


Figure 1: Kaplan-Meier curve for probability of death for TB-HIV co-infected and HIV mono-infected PLWHA over 24 months.

Predictors of death

A multivariate analysis for the predictors of death was done for the entire study. One of the findings was that the group was not a predictor of death [HR 0.84 (95% CI: 0.51-1.39) $p = 0.503$], (Table 3). The risk of death was increased if there was a $CD4 < 50$ cells/ mm^3 as compared to $CD4 > 200$ cells/ mm^3 [HR 3.17 (95% CI: 1.47-6.85) $p=0.003$] and PLWHA who were enrolled into the programme with WHO stage 4 conditions were at high risk of death [HR 3.04 (95% CI: 1.84-5.03) $p<0.001$]. Adjusted proportional hazards regression analysis showed that men had a two-fold higher risk of death compared to women [HR 1.99 (95% CI: 1.17-3.38) $p=0.011$].

Table 3: Multivariate analysis of the predictors of mortality for the study

| Variable at ART initiation | | Univariate | | | Multivariate | | |
|--|--------------------|------------|-----------|---------|--------------|-----------|---------|
| | | HR | 95% CI | p-value | HR | 95% CI | p-value |
| Group (ref: HIV mono-infected) | TB-HIV co-infected | 1.00 | 0.63-1.59 | 0.996 | 0.84 | 0.51-1.39 | 0.503 |
| Gender (ref: women) | Male | 2.00 | 1.24-3.21 | 0.004 | 1.99 | 1.17-3.38 | 0.011 |
| Age (per 5 year increase) | | 0.97 | 0.84-1.12 | 0.672 | 0.91 | 0.77-1.08 | 0.274 |
| CD4+ cell count (ref:>200), cells/mm³ | <50 | 3.64 | 1.82-7.28 | <0.001 | 3.17 | 1.47-6.85 | 0.003 |
| | 50-200 | 1.56 | 0.81-3.01 | 0.181 | 1.86 | 0.91-3.82 | 0.090 |
| Viral load (log₁₀ copies/ml) | | 1.16 | 0.86-1.57 | 0.341 | 0.90 | 0.65-1.23 | 0.499 |
| WHO stage (ref: 1-3) | Stage 4 | 3.59 | 2.25-5.74 | <0.001 | 3.04 | 1.84-5.03 | <0.001 |
| Past history of TB (ref: No) | Yes | 1.19 | 0.73-1.94 | 0.492 | 1.03 | 0.61-1.73 | 0.917 |

The analysis on adverse event (AE) looked at total number of adverse events seen by both nurses and medical officers and nurse referrals to medical officer in both groups. There was a total of 1867 AE with 968 from 404 in the TB-HIV co-infected and 899 from 410 in the TB-HIV mono-HIV infected group. There were doctor referrals of 963 from 370 in the TB-HIV co-infected and 808 from 338 in the mono-HIV infected group.

The adverse events were categorised according to anatomical systems: respiratory, ear nose and throat (ENT), gastrointestinal (GIT), cardiovascular (CVS), central nervous system (CNS), anal, genitourinary (GUT), oral and mouth, ophthalmic and others (HIV nephropathy, TB-IRIS, HIV

arthroplasty, peripheral neuropathy, TB lymphadenitis and lymphoma). The most common AE seen for both TB-HIV and HIV mono-infected groups were peripheral neuropathy, rash, TB-IRIS and oral thrush (Table 4).

The most common reason for referrals for TB-HIV co-infected group were peripheral neuropathy (61), rash (41) and TB-IRIS (40). The most common referrals for HIV mono-infected group were peripheral neuropathy (35), PPE (21) and URTI (20).

Table 4: The most common adverse events seen in study by either doctor or nurse, including referral to clinician for both TB-HIV co-infected and HIV mono-infected group.

| Type of AE | AE | | Referrals | |
|-----------------------------------|--------|-----|-----------|-----|
| | TB-HIV | HIV | TB-HIV | HIV |
| Respiratory | | | | |
| Lower respiratory tract infection | 30 | 24 | 17 | 20 |
| ENT | | | | |
| Upper respiratory tract infection | 59 | 74 | 17 | 21 |
| GIT | | | | |
| Hepatitis | 3 | 2 | 3 | 1 |
| CNS | | | | |
| Meningitis | 4 | 0 | 3 | 0 |
| Cardiovascular | | | | |
| Pericarditis | 1 | 2 | 1 | 2 |
| Ophthalmology | | | | |
| Conjunctivitis | 4 | 2 | 1 | 0 |
| Skin | | | | |
| Rash | 41 | 30 | 41 | 14 |
| Papular pruritic eruptions | 24 | 19 | 24 | 21 |
| Herpes zoster/shingles | 8 | 7 | 5 | 6 |
| Anal | | | | |
| Anal fistula/fissure | 0 | 2 | 0 | 2 |
| Genitourinary | | | | |
| Urinary tract infection | 15 | 19 | 12 | 7 |
| Oral and mouth | | | | |
| Oral thrush | 23 | 25 | 22 | 20 |
| Other | | | | |
| Peripheral neuropathy | 61 | 35 | 61 | 35 |
| TB IRIS | 39 | 13 | 40 | 11 |

The reasons for study participants in this cohort terminating their involvement in the study included death, defaulting treatment, relocating, terminating for personal reasons and other reasons.

Discussion

The World Health Organisation introduced task shifting for the initiation and management of ART from medical officers to nurses in resource constrained countries in 2008. ² Integrating task shifting for the initiation and management of ART enables more patients to be treated and managed in the healthcare system. This is critical in resource constrained countries, like South Africa.

Our study looked at the effectiveness of NIMART in an NGO setting with the assistance of medical officers for referral of PLWHA by focusing on TB-HIV co-infection vs HIV mono-infection and complexities associated with the dual diseases. The key objectives of the study was to compare the clinical outcomes, mortality and reasons for referral in two groups of PLWHA – one with Tuberculosis with HIV (TB-HIV) and the other with HIV mono-infection in a NGO funded , NIMART programme in KZN, South Africa.

The clinical outcomes of our study showed no overall difference in CD4 count increase and viral load suppression between the TB-HIV co-infected and HIV mono-infected PLWHA. Naranbai *et al.* demonstrated a rise in CD4 count in their NIMART programme from baseline and between 88.9-97.4% of the PLWHA had maintained their virologic suppression until 60 months. ⁶The STRETCH trial done in SA showed that there was no difference in viral load suppression between nurse led and doctor led groups in the cohort that was initiated by doctors and followed up by nurses, however in cohort run by nurses alone there was sub optimal viral load suppression. ⁵

Mortality rate among PLWHA who were HIV mono-infected was slightly higher than for those who were TB-HIV co-infected with in our study. A possible explanation the MR was higher in mono-infected could be due to undiagnosed TB. However, these mortality rates were not significantly different. Naranbai *et al.* also reported significant decrease in mortality by 24 months for PLWHA being monitored by nurses. ⁶ The STRETCH trial showed there was no significant difference in mortality in the cohort one (CD4 below or equal to 350 per μL .) for both the intervention and control group, however in cohort two (PLWHA with CD4 < 200 per μL .)

there was a decrease in mortality in intervention group as compared to the control group (HR 0.76, 95% CI 0.60-0.97).⁵

The predictors of death in our study were PLWHA who were enrolled with CD4<50 cells/mm³, male gender and WHO stage 4 condition into the programme. These parameters are in keeping with another study done in Durban, SA that looked at predictors of mortality in PLWHA starting ART. This retrospective cohort study showed the predictors of death were poor laboratory markers (CD4< 50µL, haemoglobin count less than 8g/dl) and clinical parameters such as a history of oral thrush and cryptococcal meningitis.⁸ The study also confirmed that a history of TB was not a significant predictor of death, a finding that was consistent with our study (p=0.917 for past history of TB).⁸ The male gender as a predictor of death is contrary to other studies. A study done by Dominique et al on HIV-TB infected PLWHA showed that the female gender is an independent risk factor of mortality.¹⁶ A further study in Ethiopia on PLWHA with HIV-TB showed that female sex workers was also seen as a predictor of death.¹⁷

The adverse events seen were consistent with PLWHA on TB and HIV treatment. Majority of referrals (963) were from TB-HIV co-infected. A study done on nurse queries in the NIMART programme revealed that the most common queries to the call centre was on laboratory result interpretation before ART initiation, 18% on adverse drug reactions and 7% on TB co-infection.⁹ Green *et al* reported a low level of referrals to medical officers from nurses in their study and cited that a possible reason was that there was a low level of medical officer presence in the clinics.⁷ Contrary, our study showed a high level of referral most likely due to presence of a medical officer on a permanent basis and in some cases the scripting of schedule medication such as fluconazole for resistant oral thrush may have prompted the nurses to refer these PLWHA.

We recognise the limitations of our study, which were that not all case report forms had diagnosis for PLWHA and as such only symptoms were reported, all laboratory toxicities were not captured as such these tests could not be evaluated from data captured. Sick PLWHA may have been triaged by sister in charge to medical officers before even being seen by a nurse thus

limiting nurse's knowledge on their management, the data was limited to an NGO clinic with no comparison to a DOH clinic.

Conclusion

In conclusion the findings of this study supports the WHO concept of task shifting and the STRETCH trial finding on effectiveness of the NIMART programme with regards to clinical outcomes and mortality. Our study showed that the NIMART is effective for PLWHA that are TB-HIV co-infected as it is for mono-infected patients when access to a medical officer for referral is available. We recommend training on ART related adverse events on dual therapy should be conducted regularly to equip nurses with knowledge and confidence to treat these events.

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Chapter 4

4 Synthesis, limitations, conclusion and recommendations

In this chapter I will present some additional results from the study (synthesis) that could not be included in the journal article, the limitations of the study, assess validity with possible bias as well as the conclusions and overall recommendations additional to those that are presented in the journal article.

The World Health Organisation introduced task shifting for the initiation and management of ART from medical officers to nurses in resource constrained countries in 2008. ⁶ South Africa introduced task shifting in 2010 when the Nurse Initiated Management of Antiretroviral Therapy programme was rolled out. ^{4,5} The STRETCH trial provided evidence of the efficacy of task shifting in South Africa. ¹¹ Our study which used an observational analytic cohort study design looked at the effectiveness of NIMART in an NGO setting with the assistance of medical officers for referral of PLWHA with complications of their therapy. A total of 1096 ART naïve participants, 474 HIV-TB co-infected and 622 HIV mono-infected were included in the study. Both groups were initiated on a once daily ART regimen (3TC, EFV, DDI/TDF) by two professional nurses during the study period. Once the programme lifespan of this NGO sponsored programme had been reached (18-24 months from initiation of ART) those PLWHA who had been stabilized on therapy were transferred to neighbouring government clinics to continue with the management of their HIV infection.

Additional data for discussion

The reasons for study participants in this cohort terminating their involvement in the study included death, defaulting treatment, relocating, terminating for personal reasons and other reasons (Table 5). Most participants [402(84.8%) HIV-TB co-infected and 544(87.5%) HIV mono -infected] were transferred to neighbouring government clinics to continue with their care. Slightly higher numbers of PLWHA defaulted treatment in the HIV-TB co-infected group when

compared to the HIV-monotherapy group [18 (3.8%) vs 13 (2.1%)], however, this was not statistically significant. This finding is clinical significant as it could be related to possible side effects and pill burden of both treatments that could explain the reason for defaulting treatment.

Table 5: Reasons for termination of TB-HIV co-infected and HIV mono-infected from the study

| Reason for termination | TB-HIV co-infected N=474 | n% | HIV mono- infected N=622 | n% | p-value |
|-------------------------------|---|-----------|---|-----------|----------------|
| Death | 35 | 7.4 | 39 | 6.3 | 0.469 |
| Defaulted | 18 | 3.8 | 13 | 2.1 | 0.100 |
| Relocated | 5 | 1.1 | 13 | 2.1 | 0.164 |
| Transferred | 402 | 84.8 | 544 | 87.5 | 0.215 |
| Patient decision | 5 | 1.1 | 8 | 1.3 | 0.786 |
| Other | 9 | 1.9 | 4 | 0.6 | 0.088 |

Limitations

The limitations of the study are categorised as limitations related to measurement validity, statistical conclusion validity, internal validity which looks at bias and confounding as well as external validity.

4.2.1.1 Measurement validity

The analysis was done from information stored in an electronic data base. The data collected from CRF was quality reviewed by a data capturer before they were submitted to the electronic data base. The data management team did a second level of checking of the CRF before the information was stored in data base as part of quality control for the CAT programme.

Not all case report forms had diagnosis for PLWHA and as such only symptoms were reported. Laboratory results for liver function, full blood count, urea and electrolytes, amylase, lipase and hepatitis B were not captured on the CRF. Hence laboratory toxicities for these tests could not be evaluated from data captured unless the prescriber felt it needed to be reported.

4.2.1.2 Statistical Conclusion validity

Statistical validity was maintained by initially choosing a sample size of 748 PLWHA with a power of 80% to detect a difference between 5.1% and 10.7% mortality among HIV mono-infected and TB-HIV co-infected PLWHA respectively. This was based on the available literature on mortality concerning TB-HIV co-infected and HIV mono-infected PLWHA. We then decided to use a sample size of 1000 which increased the power to 85%, however, we finally settled on including all the PLWHA (1096) for the study period as the data was readily available.

4.2.1.3 Internal validity

Selection Bias:

The chance of selection bias was minimised as the study sample comprised a census of all the PLWHA recruited to be part of the CAT programme for the period of Jan 2010 to Dec 2012 in a single NGO funded clinic. However selection bias did occur as there were PLWHA that did not complete follow up for the entire 24 months due to reasons of defaulting treatment, relocated to other areas, left the clinic on their own volition and for some other – non HIV related reasons. This would have resulted in non-differential misclassification which would have reduced the sample size (precision) which would have reduced the level of association towards the null.

Information Bias

Although the CRF'S were quality reviewed before being entered into the electronic data base the chance of information bias does exist as data was only verified from one source and depended on attending medical officers or nurse perspective as to what was important to transcribe on the CRF. Laboratory results for CD4 count and viral load were based on validated sensitive and specific laboratory tests from an accredited laboratory.

4.2.1.4 Confounders

The multivariate analysis for predictors of death accounted for possible confounders. The possible confounders we adjusted for were gender, age, CD4 count, VL, WHO stage and past history of TB. Other unmeasured confounders that could be analysed are social factors such as poverty, unemployment, overcrowding and comorbid conditions such as diabetes, and autoimmune disease.

4.2.1.5 External validity

The advantage of this observational study is that it allowed a direct observation of the PLWHA and clinic staff in a setting that was not manipulated by rules bound to a randomised clinical trial. The programme had special teams called trackers to locate patients that missed their visit irrespective of which cohort they were in. This study however was conducted in an NGO setting with adequate funding and staffing with a possibility that the results may not be generalised to all clinics as it lacked a comparison to Department of Health clinics.

Recommendations

Our study was an observational, retrospective study which if allowed to do it again we would change a few aspects described below.

Despite the limitations with an NGO setting, NGOs' have the freedom and financial support to provide sustainable models of care and innovation.

Study design

The retrospective study limited us in available data from CRF and cannot accommodate for missing data. We recommend a prospective study with set variables with a specifically designed CRF to collect data required as well as a comparison with a Department of Health clinic. We also

recommend a pilot study be done to which can assist with design of CRF and aid in reducing information bias. We, however, did not do this for our study.

Data Collection and interpretation

In an effort to reduce information bias the CRF would be designed to reflect final diagnosis, set laboratory test abnormality outside of CD4 count and VL, referrals to hospital with details on the hospitalization. Data verification can be conducted with dual data sources NIMART log sheets and CRF.

The recommendations for study design and data collection highlight the need for further more detailed research.

Recommendation to health services

Our study showed that the NIMART is effective for PLWHA that are TB-HIV co-infected as it is for mono-infected patients when access to a medical officer for referral is available.

Regular training on ART related adverse events on dual therapy should be conducted regularly to equip nurses with knowledge and confidence to identify and treat these events.

Conclusion

The study evaluated all PLWHA for period of two years with an initial hypothesis that NIMART management of TB-HIV co-infected patients requires complex clinical care, is associated with adverse clinical outcomes and warrants referral to medical officers as compared to HIV mono-infected patients. However, our study showed that the mortality rate in both groups were similar, clinical outcomes improved by 6, 12, 18 and 24 months in both groups and nurses referred more adverse events to the medical officers for the TB-HIV co-infected group. A nurse run programme is compatible for dual diseases, but certain conditions require referral to medical officers.

Summary

This chapter focused on findings that were not discussed in the journal article as well as the study limitations, conclusion and recommendations. The statistical analysis for our study included a descriptive and analytical component. The reasons for termination showed no statistical significance, however clinical significance can be derived for there being a higher number of defaulters in the TB-HIV group. The possible reasons for defaulting treatment can be related to side effect of both treatments as well as a high pill burden. We recognise the limitations of our study which were that not all case report forms had diagnosis for PLWHA and as such only symptoms were reported, all laboratory results outside of CD4 count and VL were not captured, the data was limited to an NGO clinic with adequate financial support with no comparison to a DOH clinic. This study showed that the NIMART is effective for PLWHA that are TB-HIV co-infected as it is for mono-infected patients when access to a medical officer for referral is available. We recommend that regular training on ART related adverse events on dual therapy should be conducted to equip nurses with knowledge and confidence to identify and treat these events.

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6 Annexures

Protocol

Research Study Protocol

Title of Research Study: Comparing the outcomes of nurse initiated management of antiretroviral therapy (NIMART) in TB- HIV co-infected patients vs HIV mono-infected patients in an urban non-government organization funded clinic in KwaZulu-Natal (KZN), from Jan 2011-Dec 2012

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Role: Director of CAPRISA Aids Treatment Programme

Signature:

A handwritten signature in black ink, appearing to read 'Kogielum Naidoo', written in a cursive style.

Purpose of Protocol

This protocol is submitted in partial fulfilment of the requirement for the Master of Public Health. The research component comprises 50% of the degree. The protocol will be submitted for ethical review to the Biomedical Research Ethics Committee (BREC) for expedited ethical approval. The study has existing ethical approval from BREC.

Summary

Background

Thirty Five million people are living with Human Immunodeficiency Virus (HIV) globally of which 25 million are in sub-Saharan Africa. The World Health Organization (WHO) in its efforts to reduce mortality introduced the concept of universal access to treatment for HIV by 2015. The concept of task shifting from skilled personal such as doctors to less skilled personal such as nurses was introduced in resource constrained countries. South Africa initiated its policy in September 2010 that allowed the provision of antiretroviral medication to HIV infected patients by primary health care nurses.

The purpose of the study is:

To compare outcomes of nurse initiated management of antiretroviral therapy (NIMART) in TB- HIV co-infected patients vs HIV mono-infected patients in an urban non-government organization funded clinic in KwaZulu-Natal (KZN), from Jan 2011-Dec 2012.

The specific objectives of this study are:

1. To describe and compare the patient demographic variables and the HIV and AIDS disease profile in TB-HIV co infected patients' vs HIV mono- infected patients.
2. To analyze the difference between TB -HIV co-infected and HIV mono- infected patients with regards to:

- Reasons for referrals of NIMART patients to the medical officer
- Clinical outcomes
- Laboratory outcomes
- Mortality

Research Methods

The study is an observational, retrospective, analytical, cohort study. The study will be conducted at an urban NGO clinic in KZN, looking at HIV-TB co infected patients and HIV mono-infected patients (sample of 1000 patients). Data will be analyzed from case report forms; patient folder review and NIMART log sheets from nurses. Data analysis will incorporate both a descriptive and an analytical component.

Table of Contents

| | |
|--|----|
| <u>Purpose of protocol and summary</u> | 3 |
| Acronyms and Abbreviations | 7 |
| 1.Introduction..... | 8 |
| 2.Literature review | 9 |
| 3. Purpose of the study | 12 |
| 4. Specific Objectives | 14 |
| 5. Type of research..... | 14 |
| 6. Definitions..... | 14 |
| 7. Research Methods | 14 |
| 7.1 Study Setting | 15 |
| 7.2 Study Design..... | 15 |
| 7.3 Study population | 15 |
| 7.3.1 Inclusion / Exclusion Criteria | 16 |
| 7.4 Study Sample | 16 |
| 7.4.1 Method of selecting sample | 16 |
| 7.4.2 Size of sample | 16 |
| 7.5 Data sources | 17 |
| 7.5.1 Measurement instruments and data collection techniques | 17 |
| 7.6 Measures to reduce selection bias and information bias | 17 |
| 7.7 External Validity / Generalizability | 17 |

| | |
|--|----|
| 7.8 Pilot study | 18 |
| 7.9 List of Variables..... | 18 |
| 7.10 Plan for Data handling/processing | 18 |
| 7.11 Statistical methods | 19 |
| 7.11.2 Analytic statistics | 19 |
| 7.12 Summary of objectives, data collection and type of data analysis..... | 20 |
| 7.13 Study limitations | 21 |
| 8. Ethical Considerations | 21 |
| 8.1 Institutional Ethical Review Board..... | 21 |
| 9. Work Plan | 21 |
| 9.1 Budget..... | 21 |
| 9.2 Study Period/Timelines..... | 21 |
| 10. Acknowledgments..... | 22 |
| 11.References | 23 |
| 12. Appendices..... | 26 |
| <u> </u> Appendix 1 | 26 |
| <u> </u> Appendix 69 | 26 |

Acronyms and Abbreviations

| | |
|----------------|--|
| NIMART | Nurse Initiated Management of Antiretroviral Therapy |
| HIV | Human Immunodeficiency Virus |
| AIDS | Acquired Immune Deficiency Syndrome |
| WHO | World Health Organisation |
| TB | Tuberculosis |
| ART | Antiretroviral Therapy |
| SA | South Africa |
| DOH | Department of Health |
| TAC | Treatment Action Campaign |
| PLWH | People living with HIV |
| Up | Microliter |
| RCT | Randomised Control Trial |
| NGO | Non-Government Organisation |
| KZN | Kwa Zulu -Natal |
| CAPRISA | Centre for Aids Prevention Research in South Africa |
| CAT | CAPRISA Aids Treatment |

1. Introduction

Thirty Five million people are living with HIV globally of which 25 million are in sub-Saharan Africa .¹ Approximately 5 million people are living with HIV in South Africa (SA) ¹. Globally there were 2.1 million new infections by the end of 2013 .¹

Since the discovery of HIV in 1981 an estimated 39 million people have died from Acquired Immune Deficiency Syndrome (AIDS).²

The World Health Organization (WHO) in its efforts to reduce mortality introduced the concept of universal access to treatment for HIV by 2015, which also encompasses Millennium Development Goal 6 .³ This goal is focused on combating HIV, AIDS, malaria and other diseases .³ The WHO global health strategy was implemented to achieve universal access to treatment and encompasses “reduce new infections by 50 percent among young people (15-24 years), reduce tuberculosis (TB)-related mortality by 50 percent, eliminate new infections in children, and reduce HIV-related mortality” .³

Access to universal treatment is not as simple as starting all eligible patients on treatment and involves challenges such as wide scale treatment access, trained healthcare staff, patient adherence, life -long commitment to treatment and provision of effective antiretroviral therapy (ART) .³

It is estimated that in Europe there are 8 times more nurses and 15 times more doctors than Africa .³ There are several reasons that exist for shortage of staff in poorer countries such as the incentive of working in wealthier countries and exposure to HIV. ³

Primary health care nurses provide health care to thousands of patients both in rural and urban regions of SA and are a valuable resource for providing education, support and care for communities. ^{4,5}

These nursing practitioners often work under circumstances where access to a medical doctor is a scarce commodity and have to utilize their experience, skill and knowledge to provide a good quality of service to patients .^{4,5}

The national government in SA had initiated a policy in September 2010 that allowed the provision of antiretroviral medication to HIV infected patients by primary health care nurses .^{4,5}

It is evident that there are many challenges and lessons that can be learned from an established nurse based roll out program for ART.

2. Literature Review

The following section describes the background to the NIMART strategy, highlighting the need to overcome clinical staff shortages and initiatives to achieve the millennium development goals with regard to HIV rollout. The clinical trial summaries reflect the outcomes of various NIMART programmes and task shifting.

2.1. The World Health Organisation strategy

In 2008 the burden of HIV was expanding globally and the lack of highly trained personal to administer the treatment, lead the WHO to provide a global recommendation of task shifting.⁶ This was proposed with aim of overcoming the shortages of staff and being able to provide increased access to ART and meet the Millennium Development Goals.^{6,8} The Sub-Saharan region was most affected with the HIV epidemic and thus task shifting would prove to be beneficial here.⁷

2.2. Task shifting

Task shifting involved the transference of certain tasks which were performed by highly skilled personal such as doctors to less skilled personal such as nurses.⁶ Task shifting has been shown in studies to allow higher access to HIV services with a result of greater efficiency of service delivery.⁸ For example, the number of HIV treatment initiations due to task shifting doubled in Malawi.⁷ In Uganda there was an increase in enrolment of patients onto ARV program by 19.7%.⁷ Task shifting was implemented in South Africa in 2010.³

2.3. National strategic plan and NIMART

South Africa has a quadruple burden of disease which comprise of communicable diseases such as HIV/AIDS and TB, maternal and child morbidity and mortality, non- communicable disease as well as violence, injuries and trauma.⁹

In line with the Millennium Development Goal 6 of combating HIV/AIDS, malaria and other diseases, and to address the SA burden of disease, the national strategic plan 2009-2014 for health was developed.^{3,9} One of the imperatives was to speed up the implementation of HIV / AIDS and Sexually Transmitted Infections National Strategic Plan from 2007-11 with an increase focus on TB and other communicable diseases.⁹ Analysis of South Africa s' challenges led to the realization that HIV was a major contributor to morbidity and mortality and action needed to be taken to improve this outcome.⁹ Thus the government rolled out the NIMART program in 2010.⁹ From 2010 to 2013 the number of people initiated on treatment increased from 923 000 to 1.9 million.⁹ The goal in South Africa is to achieve a HIV/AIDS free under 20 generation by 2030 as stipulated in National Development Plan.⁹

2.4. Department of health (DOH) ART guidelines

In South Africa the decade of HIV denialism was countered through the actions of the Treatment Action Campaign (TAC) who exerted pressure on the existing South African government to provide treatment and care for people living with HIV and AIDS (PLWHIV) .¹⁰ In 2010 ARV treatment was provided to all PLWH that had a CD4 count of 200 cells per microliter (up) or less, with the exclusion of TB co-infected and pregnant females who were initiated on treatment with higher counts of 350 cell/up. ¹⁰

By 2011 the guidelines were updated for ARV initiation to include all PLWH to start at CD4 counts of 350 cells/ul or less. ¹⁰ By 2013 the guidelines were updated once again to initiate treatment with Antiretroviral drugs irrespective of their CD4 for PLWH co- infected with TB and all pregnant women.¹⁰ The massive shift in initiating ARV treatment at an earlier CD4 count meant a scale up of HIV treatment programmes that required trained personal .¹⁴

2.5. Evidence on NIMART

The STRETCH trial which is interpreted as “Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa” was a parallel, cluster randomised controlled trial (RCT) conducted in 16 public sector clinics in the Free State during the period of 2008 to 2010 .¹¹ There were two cohorts of patients, patients waiting to start treatment and patients already on ART.¹¹ The two cohorts deferred in terms of primary outcomes. Cohort one had an outcome of time to death and cohort two was undetectable viral loads 12 months after enrolment .¹¹ Cohort one had 9252 participants and cohort two had 6231 participants .¹¹ The results revealed that patients in cohort one had a 47% lower chance of death if they were on ART than those who were not and the study was able to attain the goal of viral load suppression in patients on treatment.¹¹ This trial has demonstrated that task shifting is possible and that ART initiation and follow up can be done safely with nurses .¹¹ Another RCT by Sanne *et al.* looking at nurse verse doctor management of HIV infected person also concluded that there was no significant difference in mortality and virological failure. ¹²

2.6. Sustainability of NIMART

The success of NIMART has been proven in both the public sector as well as in non-government organisations (NGO'S) with private funding. A study done by Naranbhai *et al.* conducted in a rural HIV clinic in KZN, showed that task shifting was able to influence positive long term treatment Outcomes .¹³ This study was conducted from 2004 to 2010, however the nurses were not involved in ART initiation but rather in the follow up of treatment initiated patients. ¹³ There was an onsite doctor for ART initiation and management of complications .¹³. Virological suppression was achieved in 89-97% of patients for period of 60 months and there was 82% retention even after 24 months .¹³

Another cross sectional quality of care study in Khayelitsha in 2011 to 2012 showed that a clinical mentorship program improved clinical skills of nurses and boosted their confidence .¹⁴ The South African government has since set a target of 85% for NIMART by 2016 .¹⁴

A study conducted by the Foundation of Professional Development (FPD) in seven provinces in SA between 2010 and 2011 looked at the amount of nurses that were implementing NIMART within two months of patient's attending the clinic. In addition quality of care and barriers to NIMART were evaluated. ^{14,15} The results indicated that only 72 % of nurses initiated treatment .¹⁴ Barriers identified included lack of mentorship; training in pharmacology; clinical skills and shortage of primary health care nurses. ¹⁵

The challenges highlighted within the above trials provide an insight as to the operational challenges we have to overcome in the implementation of these Programmes in South Africa.

3. Purpose of the study

To compare outcomes of nurse initiated management of antiretroviral therapy (NIMART) in TB- HIV co-infected patients vs HIV mono-infected patients in an urban non-government organization funded clinic in KwaZulu-Natal (KZN), from Jan 2011-Dec 2012.

Hypothesis: NIMART management of TB-HIV patients is more complex to manage as compared to HIV mono-infected patients, thus warranting referral to a medical officer.

4. Specific Objectives

The following section identifies the specific objectives of the study which include both the description profile within a NIMART Programmed as well as an analysis of differences between the two cohorts.

The specific objectives of this study are:

- 4.1 To describe and compare the patient demographic variables and the HIV and AIDS disease profile in HIV-TB co infected patient's vs HIV mono- infected patients.
- 4.2 To analyze the difference between TB -HIV co-infected and HIV mono- infected patients with regards to:
 - Reasons for referrals of NIMART patients to the medical officer
 - Clinical outcomes
 - Laboratory outcomes
 - Mortality
 -

5. Type of research

Health system research with population based epidemiological component

6. Definitions

The definitions listed below indicate specific definitions and how these would apply in the study:

- NGO is defined as a non -government organization or non for profit organization. The Term NGO used in this study refers to the center that has conducted the research within their urban site at EThekwini;
- TB Staging: The current clinical classification system for TB is based on the pathogenesis of the disease. In this study the Centre for Disease classification will be used;
- HIV WHO Staging: The WHO classification of HIV for adults and adolescents will be used for the purpose of this study. We will consider this in the present document, the category of adults and adolescents aged 15 years and over for surveillance purposes;
- Urban: Relating to, characteristic of, or constituting a city. For the purpose of the study the word urban refers to the setting in the city of Durban;
- Rural: Rural Health Clinics must be located in communities that are both rural and underserved. References made to Rural Health Clinics, apply to those clinics outside the city on in Non-urbanized areas;
- STATA: This is licensed statistical software used by statisticians for the purpose of statistical analysis.

7. Research Methods

The following section describes the research setting, methodology of sampling as well as data collection components required for data analysis. The statistical components for analysis are reviewed under this section as well.

7.1 Study Setting

The study setting is an urban NGO clinic in KZN. The eThekwini clinic is part of the NGO CAPRISA (Centre for Aids Prevention Research in Southern Africa). The rollout program for the CAPRISA AIDS treatment (CAT) began in 2004 as an initiative to support the overburdened public sector to care for HIV infected patients.

Patients were actively recruited from the DOH clinics situated next to the eThekwini clinic, where the staff offered voluntary counselling and HIV testing for patients visiting the clinic. Patients that tested HIV positive were extensively counselled and offered a CD4 count and an opportunity to join the antiretroviral rollout program which involved a network of support structures, counselling and antiretroviral provision as well as treatment and investigation of opportunistic infections.

The antiretroviral provision had been initially done by doctors with the role of primary health care nurses reviewing patients clinically to assess eligibility and attending to clinically stable patients after six months on antiretroviral therapy. This trend had changed in 2010 in line with the national health department's policy allowing nurses to initiate antiretroviral therapy.

7.2 Study Design

This study is an observational, retrospective, cohort study with an analytic component.

7.3 Study population

The study population consists of TB-HIV co-infected and HIV mono- infected patients initiating ART at an urban NGO clinic in KZN from January 2011 to December 2012 by nurses.

7.3.1 Inclusion / Exclusion Criteria

7.3.1.1 Inclusion criteria:

- Adult patients age >18
- Newly initiated patients on ART

7.3.1.2 Exclusion criteria:

- Patients <18
- Patients already on ART
-

7.4 Study Sample

The sample will be adult TB-HIV co-infected and HIV mono-infected patients initiated on ART.

7.4.1 Method of selecting sample

Simple random sampling will be performed for the selected patients. Patients will be sampled from the total number of patients initiated between January 2011 and December 2012 by two nurses.

7.4.2 Size of sample

The sample size is 1000 patients. Based on the literature on mortality concerning mono HIV infected and TB-HIV co-infected patients. We estimated a sample size of 748 with a power of 80% to detect a difference between 5.1% and 10.7% mortality among mono HIV infected and TB-HIV co-infected patients respectively. However, we decided to use a sample size of 1000 because the data was readily available. A sample size of 1000 increased the power to 85%.

7.5 Data sources

7.5.1 Measurement instruments and data collection techniques

The data sources that will be reviewed are:

- Case report forms in data fax;

- Laboratory results;
- Patient folder review; and
- NIMART log sheets captured by nurses.

The above data sources have demographic, clinical, laboratory and pharmacological information which will be analyzed statistically.

7.6 Measures to reduce selection bias and information bias

The possible biases in study are:

- Selection bias and we have planned on simple random sampling to overcome this bias.
- Information bias and we have planned to conduct the retrospective review from 3 different data sources to verify the data and overcome this bias.
- There will be no sample replacement with missing data and this will be accounted for in the analysis.
-

7.7 External Validity / Generalizability

The reliability of data is maintained through simple random sampling and the results of the study can be generalizable to other similar urban communities in KwaZulu -Natal.

7.8 Pilot study

There will be no pilot study conducted.

7.9 List of Variables

The following list of variables is considered for the study:

- Patient: Age, race, sex, residence, female-pregnancy status;
- Opportunistic infection staging for TB: The current clinical classification system for TB is based on the pathogenesis of the disease;
- Disease staging for HIV: The WHO classification of HIV for adults and adolescents will be used for the purpose of this study. We will consider the category of staging for adults and adolescents aged 15 years and over;
- Laboratory: Creatinine and creatinine clearance, haemoglobin, alanine aminotransferase (ALT), CD4 count and viral load at baseline, six months and twelve months;
- Reasons for medical officer referrals;
- Clinical : Adverse events, hospitalization, new opportunistic infections;
- Mortality
- Laboratory outcomes: (CD4 count and Viral load at baseline, six months and twelve months);
- Incidence: Initiations of ART in both groups, failure to treatment.

7.10 Plan for Data handling/processing

Data will undergo data quality checks by researcher and the co-investigator.

7.11 Statistical methods

7.11.1 Descriptive statistics

7.11.1.1 Data on patient characteristics

The following data will be collected:

- Age, sex, race, residence;
- Laboratory results: creatinine and creatinine clearance, haemoglobin, alanine aminotransferase, CD4 count, viral load;
- Pregnancy status;
- The WHO stage;
- The TB stage

The data description will include measures of central tendency such as the mean as well as measures for dispersion which will be the interquartile range.

7.11.2 Analytic statistics

The variables for the analysis for both the TB-HIV co-infected patients and HIV-mono infected patients are:

- Reasons for medical officer referrals
- Clinical outcomes(adverse events, hospitalisation ,new opportunistic infections)
- Mortality
- Lab outcomes(CD4 count and viral load baseline,6 and 12 months),

The unpaired T test will be included for continuous data, and the Fisher's exact test for categorical data.

Proportional- hazards regression models are to be used to adjust for confounding variables.

Mortality will be analysed using the Kaplan-Meier curve and log-rank test.

STATA software will be used where appropriate.

7.12 Summary of objectives, data collection and type of data analysis

The section below summarizes the study objectives as well as the data collection and analysis.

The specific objectives of this study are:

1. To describe and compare the patient demographic variables and the HIV and AIDS disease profile in HIV mono- infected patients vs HIV-TB co infected patients
2. To analyze the difference between TB -HIV co-infected and HIV mono- infected patients with regards to:
 - Reasons for referrals of NIMART patients to the medical officer
 - Clinical outcomes
 - Laboratory outcomes
 - Mortality

Data collection will be from case report forms; patient folder review and NIMART log sheets from nurses. Simple random sampling will be done to overcome selection bias. The statistical analysis will consist of descriptive aspects which encompass patient characteristics. The analytical component which will include the, unpaired T test for continuous data and the Fisher's exact test for categorical data. The proportional-hazards regression models will be used to adjust for confounding variables. Mortality will be analyzed using a Kaplan-Meier curve and log-rank test. STATA software will be used where appropriate.

7.13 Study limitations

The data is limited to an NGO clinic that has adequate financial support with no comparison with a DOH clinic.

Once the data has been analyzed, key findings and recommendations for the NIMART Programme will be able to be concluded.

8. Ethical Considerations

The following sections consider ethical components required prior to and during the conduct of the study:

8.1 Institutional Ethical Review Board

This is a retrospective review of existing data thus no informed consent will be required, however relevant approvals need to be documented prior to commencement with the study analysis.

9. Work Plan

The following section indicates processes in the work plan to conduct the study. These include a study budget as well as timelines for accomplishing key milestones.

9.1 Budget

Please refer to appendix 1 for budget. The budget set also assesses final variance from budget and will further be broken down at a later stage into a monthly costing.

9.2 Study Period/Timelines

Please refer to appendix 2 for study timelines.

The milestones set for each objective range from February 2015 to September 2016.

10. Acknowledgments

I would like to acknowledge my supervisor Dr Stephen Knight, my co-investigator Dr Kogielum Naidoo, CAPRISA and the patients of the CAT program for giving me the opportunity to conduct this research.

11. References

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12. Appendices

Appendix 1

Budget for NIMHAART project from June 2015 to September 2016

| SOURCE | AMOUNT |
|--------------------------------|---------------------|
| INCOME | R 0 |
| TOTAL EXPENSES | R55000 |
| ACTUAL CLAIMED | |
| TOTAL SURPLUS/DEFICIT | |
| ITEMS: | |
| DATA MANAGEMENT: | |
| 1.Data capture | R 5 000 |
| 2.Scientific writer | R 7 000 |
| 3.Statistician | R 10 000 |
| 4.Proof reader/Language editor | R 5 000 |
| Others | |
| Fuel | R 500 (5,55 per km) |

| | |
|------------------------------|-------------------------------------|
| Equipment | R 1 000 |
| Stationery | R 3 000 |
| Printing and copies | R 2 000 |
| Telephone and fax | R 2 000 |
| Postage and delivery | R 2 500 |
| Consumables | R 4 000 |
| Cell phone charges | R 5 000 (500 per month)x 10 months |
| 3G usage | R 5 000 (500 per month)x 10 month |
| Publication | |
| Journal publication | R 500 |
| Printing and binding thesis | R 2 000 |
| Printing and binding reports | R 1 000 |
| Total Expenses | R 55 000 |

Appendix 2

Table 1: NIMART study time lines

| Description | Feb-May 2015 | 19 May 2015 | Jun-Aug 2015 | Sep 2015 Jan 2016 | Feb - Apr 2016 | May-Jun 2016 | Jul 2016 | Aug 2016 | | | | Sep 2016 |
|------------------------------|--------------|-------------|--------------|----------------------|----------------|--------------|----------|----------|-----|-----|-----|----------|
| | | | | | | | | W 1 | W 2 | W 3 | W 4 | |
| Protocol development | √ | | | | | | | | | | | |
| Protocol submission | | √ | √ | | | | | | | | | |
| Development of tools | √ | | | | | | | | | | | |
| Data collection | | | | √ | | | | | | | | |
| Data analysis | | | | | √ | | | | | | | |
| Dissertation Write-up | | | | | | | | | | | | |
| Draft 1 | | | | | | √ | | | | | | |
| Draft 2 | | | | | | | √ | | | | | |
| Draft 3 | | | | | | | | √ | | | | |
| Internal | | | | | | | | | | √ | | |

| | | | | | | | | | | | | | | | |
|-------------------------------|--|--|--|--|--|--|--|--|--|--|--|--|--|--|---|
| submission | | | | | | | | | | | | | | | |
| Examination submission | | | | | | | | | | | | | | | √ |

█ *Ethic approval*



UNIVERSITY OF
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INYUVESI
YAKWAZULU-NATALI
29 February 2016

Ms N Jithoo (9500953)
Discipline of Public Health
School of Nursing and Public Health Medicine
nirakshajithoo@yahoo.com

Protocol: Comparing the outcomes of nurse initiated management of antiretroviral therapy in tuberculosis-human immunodeficiency virus (HIV) co-infected patients vs mono-infected patients in an urban non-government organization funded clinic in KZN, from January 2011- December 2012.

Degree: M-PH

BREC reference number: BE494/15 (sub-study of E248/05)

EXPEDITED APPLICATION

The Biomedical Research Ethics Committee has considered and noted your application received on 18 November 2015.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 23 February 2016 to queries raised on 12 February 2016 have been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval**.

This approval is valid for one year from **29 February 2016**. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at <http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx>.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its meeting taking place on **08 March 2016**.

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

Professor J Tsoka-Gwegweni
Chair: Biomedical Research Ethics Committee

cc Supervisor: moodleyp@ukzn.ac.za
cc postgrad: dudbrajhp@ukzn.ac.za

Biomedical Research Ethics Committee

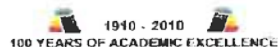
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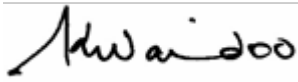
To whom it may concern,

RE: Protocol Titled “Comparing the outcomes of nurse initiated management of antiretroviral therapy in tuberculosis-human immunodeficiency virus (HIV) co-infected patients vs mono-infected patients in an urban non-government organisation funded clinic in KZN, from January 2011-December 2012 (BREC Ref. No.: BE494/15).

I hereby grant permission for the PI of the abovementioned to use stored patient records at the

CAPRISA eThekweni Clinical Research Site, located at 03 Richards Road, Durban, South Africa.

Yours Sincerely,



Dr Kogieleum Naidoo .Head of Treatment Research CAPRISA

Tel: 031 260 4687/1922

Email: Kogie.Naidoo@caprisa.org



TABLE OF CONTENTS

| | |
|-----------------------------------|------------|
| • Description | p.1 |
| • Impact Factor | p.1 |
| • Abstracting and Indexing | p.2 |
| • Editorial Board | p.2 |
| • Guide for Authors | p.3 |



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- Title page- bearing title, all authors' initials, surname, main degrees (two only) and the name and location of the institution(s) where the work was done. The author to whom proofs and correspondence should be sent should be clearly indicated with correct address, e-mail, telephone and fax details.
- Abstract. This should be structured under the following headings:

Objectives

Study design

Methods

Results

Conclusions

- Keywords. 3-6 keywords should follow the abstract
- Introduction
- Methods
- Results
- Discussion
- Acknowledgements including declarations: Statements of ethical approval, funding and competing interests (see section 9)
- References (see section 10)

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Tables

Number tables consecutively in accordance with their appearance in the text. Place footnotes to tables below the table body and indicate them with superscript lowercase letters. Avoid vertical rules. Be sparing in the use of tables and ensure that the data presented in tables do not duplicate results described elsewhere in the article.

4.3 Short communications

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A short communication is preferred for the submission of important preliminary observations or data that does not warrant publication as a full paper. Short communications should be approximately 500-1500 words in length and provide adequate information to allow for the same peer review given to other submissions.

- An abstract will be requested during the online submission process in order to facilitate peer-review, but should not be included within the manuscript.

- Keywords are not required. Specific sections, such as Methods, should not be used.

- A short communication can include one table or figure and up to 10 references. Preliminary data published as a short communication will not preclude subsequent publication of more complete results if the work is significantly expanded.

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Systematic Review papers presenting exhaustive, critical assessments of the published literature on relevant public health topics or questions will be considered. Such reviews should be prepared in strict compliance with MOOSE or PRISMA guidelines or with Cochrane's complementary guidelines for systematic reviews of health promotion and public health interventions, as appropriate. Public Health encourages authors to use alternative databases covering scientific literature from low- and middle-income countries not indexed in the traditional international databases (i.e. Medline, Web of Science). All systematic reviews need to be submitted with a supporting statement of which guideline has been used in the preparation of the review.

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References: up to a maximum of 100.

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Authors will be given the opportunity to comment and respond to any correspondence we intend to include in the 'Letters to the Editors' regarding their previously published manuscript.

4.6 Celebrating Public Health Lives

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Keywords are not required.

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Acknowledgements

Collate acknowledgements in a separate section at the end of the article before the references and do not, therefore, include them on the title page, as a footnote to the title or otherwise. List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

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