A COMPARISON OF THE EFFECTIVENESS OF PROTEASE INHIBITOR-BASED HIGHLY ACTIVE ANTI-RETROVIRAL TREATMENT REGIMENS IN TRINIDAD AND TOBAGO

By

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In the subject

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Supervisor: PROF VJ Ehlers

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DEDICATION

To my two loving children, Sean and Dhalia because of whom I developed hope. I quest to be a good example to them and would wish them to grow into hard working successful adults.

STUDENT NUMBER: 37335065

DECLARATION

I declare that **A COMPARISON OF THE EFFECTIVENESS OF PROTEASE INHIBITOR-BASED HIGHLY ACTIVE ANTI-RETROVIRAL TREATMENT REGIMENS IN TRINIDAD AND TOBAGO** is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

…… ……

Full names Date

ACKNOWLEDGEMENTS

I thank my supervisor Professor Valerie Ehlers of the University of South Africa for supporting me all through this journey. She attended to my documents several times and was very patient and understanding of many of the challenges I met during this research.

I wish to thank Dr George Legall of the University of the West Indies for helping me to analyse the data, even though I was a total stranger to him when I was referred to him. He tirelessly guided me through the process. I thank the staff of the HIV clinic of the San Fernando General Hospital for their help guiding me through the department.

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ABSTRACT

Few studies have assessed the optimum second line highly active anti-retroviral therapy (HAART) regimen in patients who had failed on the first-line HAART in resource-limited settings. This study aimed to compare the Protease inhibitor (PI)-based second line HAART regimens used in one clinic in Trinidad by comparing immunological, virological and clinical outcomes of patients on the different second line HAART regimens.

The records of 35 treatment-experienced patients, over 21years of age and on PI-based regimens for at least six months, were analysed using SPSS version 20.

The regimen containing TDF/FTC/AZT/LPV/r proved to produce superior outcomes compared to the other second line regimens.

Due the small number of usable patients' records, the findings cannot be generalised but indicate directions for future studies attempting to compare the treatment outcomes of different second line HAART regimens.

Keywords: Highly active anti-retroviral treatment (HAART), 1st HAART regimens, 2nd line HAART regimens, resistance to anti-retroviral drugs, treatment adherence

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Date

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Affection immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
AZT	Zidovudine
ATZ	Atazanavir
CDC	Centres for Disease Control
CHART	Carribean HIV/AIDS regional training network
d4T	Stavudine
ddC	Dalcitabine
ddI	Didanosine
DRV	Darunavir
EFV	Efavirenz
FDA	Food and Drug Administration
FOS-APV	Fosamprenavir
FTC	Emitricitabine
HAART	Highly active antiretroviral therapy

HIV	Human immunodeficiency virus
HTLV-1	Human T-cell leukaemia virus type 1
IDV	Indinavir
IRIS	Immune reconstitution inflammatory syndrome
LPV	Lopinavir
MOHG	Ministry of Health of Guyana
MOHTT	Ministry of Health of Trinidad and Tobago
NFV	Nelfinavir
NRTI	Nucleoside/Nucleotide reverse transcriptase inhibitors
NNRTI	Non-nNucleoside/Nucleotide reverse transcriptase inhibitors
NVP	Nevirapine
PI	Protease inhibitor
PMTCT	Prevention of mother to child transmission of HIV
RNA	Ribonucleic acid
RTV/r	Ritonavir
SFGH	San Fernando General Hospital
SQV	Saquinavir
TAM	Tymidine analogue mutations
TDF	Tenofovir
TH	T Helper
UK	United Kingdom

UNAIDS	Joint United Nations Programme on HIV/AIDS
Unisa	University of South Africa
USA	United States of America
VL	Viral load
WHO	World Health Organization

CHAPTER 1

ORIENTATION TO THE STUDY

1.1 INTRODUCTION

Human immunodeficiency virus (HIV) infections and acquired immunodeficiency syndrome (AIDS) are prevalent throughout the Republic of Trinidad and Tobago, which is an archipelagic state in the southern Caribbean, lying just off the coast of northeastern Venezuela and south of Grenada in the Lesser Antilles. It shares maritime boundaries with Barbados to the northeast, Grenada to the northwest, Guyana to the southeast, and Venezuela to the south and west. According to the Global Aids Response Trinidad and Tobago Country Progress Report (UNAIDS 2012:3), an estimated 22 787 people were living with HIV, with an estimated prevalence rate of 1.5% at the end of 2010, in Trinidad (Trinidad &Tobago 2013).

Symptoms of HIV/AIDS include diarrhoea, weight loss, oral thrush, skin rashes, tuberculosis and malignancies. Patients are grouped based on clinical presentation into World Health Organization (WHO 2010:27-28) stages 1, 2, 3 and 4, in increasing order of progression of the disease, as summarised in table 1.1.

TABLE 1.1: WHO CLINICAL STAGING OF HIV DISEASE IN ADULTS AND ADOLESCENTS.
CLINICAL STAGE 1
Asymptomatic Persistent generalised lymphadenopathy
CLINICAL STAGE 2
Moderate unexplained weight loss (under 10% of presumed or measured body weight) Recurrent respiratory tract infections (sinusitis, tonsillitis, otitis media, pharyngitis Herpes zoster Angular cheilitis (inflammation of the corners of the lip) Recurrent oral ulcerations Papular pruritic eruptions Seborrhoeic dermatitis Fungal nail infections

CLINICAL STAGE 3
Unexplained severe weight loss (over 10% of presumed or measured body weight)
Unexplained chronic diarrheoa for longer than one month
Unexplained persistent fever (intermittent or constant for longer than one month)
Persistent oral candidiasis
Oral hairy leukoplakia
Pulmonary tuberculosis
Severe bacterial infections (such as pneumonia, empyaema, meningitis, pyomyositis, bone and/or joint infection, bacteraemia, severe pelvic inflammatory disease)
Acute necrotising ulcerative stomatitis, gingivitis or periodontitis
Unexplained anaemia (below 8mg/dl), neutropenia (below 0.5 x 10^9/l) and/or chronic thrombocytopaenia (below 50 X 10^9/l)
CLINICAL STAGE 4
HIV wasting syndrome
Pneumocystic jiroveci pneumonia
Recurrent severe bacterial pneumonia
Chronic herpes simplex infection (orolabial, genital, oro-ano-rectal of more than one month's duration or visceral at any time)
Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs)
Extrapulmonary tuberculosis
Kaposi sarcoma
Cytomegalovirus disease (retinitis, or infection of other organs, excluding the liver, spleen and lymph nodes)
Central nervous system toxoplasmosis
HIV encephalopathy
Extra-pulmonarycryptococcosis, including meningitis
Disseminated non-tuberculous mycobacteria infection
Progressive multifocal leuco-encephalopathy
Chronic cryptosporidiosis
Chronic isosporiasis
Disseminated mycosis (histoplasmosis, coccidiomycosis)
Recurrent septicaemia (including non-typhoid salmonella)
Lymphoma (cerebral or B cell non-Hodgkin)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy-

Highly active antiretroviral therapy (HAART), a treatment paradigm using three or more antiretroviral (ARV) drugs in combination, has reduced the morbidity and mortality of patients with HIV/AIDS (WHO 2007), with immunological (increased CD4 counts), virological (decreased viral load counts), and clinical (improved clinical state) responses in developing countries such as Trinidad (Wools-Kaloustian, Kimaiyo, Diero, Siika, Sidle, Yiannoutsos, Musick, Einterz, Fife & Tierney 2006:41-8), similar to that in developed countries. Mc Mahon, Elliot, Bertagnolio, Kubiak & Jordan (2013) in a systematic review of studies from low and middle income countries revealed 71% of patients on the intention-to-treat analysis and 84% in the on-treatment analysis had attained viral suppression 12 months after ARV initiation and this compared favourably with outcomes in high-income countries

When first line ARVs fail, provided the patient has adhered to his/her antiretroviral therapy (ART) regimens, second line ARV combinations need to be used. The WHO (2010:53-57) states that a new second line regimen has to involve drugs that retain activity against the patient's virus strain and should ideally include a minimum of three active drugs, with at least one from a new class of ARVs, in order to increase the likelihood of treatment success and minimise the risk of cross resistance (Ministry of Health of Trinidad and Tobago [MOHTT] 2009:9).

1.2 BACKGROUND INFORMATION ABOUT THE RESEARCH PROBLEM

1.2.1 The source of the research problem

Interest in the research topic arose because of the documented need for research comparing the treatment outcomes of second line ARVs. The WHO (2010:56) guideline recommends using second line drugs depending on what was used in the first line. The MOHTT (2009:9) guidelines also state that it should be assumed that drug resistance has occurred to the components of the regimen that the patient was taking when failure was diagnosed. Good early outcomes have been observed in protease inhibitor-based second line regimens with at least one neucleoside or neucleotide reverse transcriptase inhibitor NRTI change. There is cross resistance between Lamivudine (3TC) and Emitricitabine (FTC) and the two drugs are similar in activity. Studies proving the efficacy of using either drug, after the other fails in a

previous regimen, need to be conducted to provide scientific evidence of the efficacy of specific second line ART regimens (MOHTT 2009:9; Pujades-Rodríguez, O'Brien, Humblet & Calmy 2008:1305-1312; WHO 2012:11).

The WHO (2010:53) states that few studies were identified in a systematic review, conducted with the objective of assessing the optimum second line ART regimen in patients failing first line therapy in resource limited settings. There was a need for this study to compare the second line regimens used in Trinidad (Humphreys, Hernandez & Rutherford 2010).

1.2.2 Background to the research problem

HAART medications have reduced AIDS morbidity and mortality rates (WHO 2007). HAART regimens are mostly modified in response to toxicity, intolerance, treatment failure or evidence of superiority of another regimen. Non-adherence to ARVs is a major cause of failure of any HAART regimen. Patients, proven to be adherent to first line ARVs, who show evidence of treatment failure, need to change from the first line HAART regimen to the second line regimen containing preferably three new drugs, with at least one from a new class. The Trinidad HIV/AIDS treatment and care guidelines recommend the use of the preferred first line combination in Trinidad as Tenofovir (TDF) and Emitricitabine (FTC), nucleotide and nucleoside reverse transcriptase inhibitors (NRTIs) respectively, in a once daily combination pill, Truvada, in combination with Efavirenz (EFV), a non-nucleoside reverse transcriptase inhibitor (NNRTI), also given once daily. Lamivudine is also sometimes used in place of FTC. Some patients who are intolerant of TDF due to renal toxicity are given Zidovudine (AZT) and 3TC as NRTI backbone in a combination pill, Combivir. Those unable to use AZT because of anaemia use Truvada. Patients intolerant of EFV use Nevipapine (NVP) if the CD4 count is less than 250, and a protease inhibitor (PI), either Ritonavir (r) boosted Lopinavir (LPV/r) or Atazanavir (ATV/r) when the CD4 count exceeds 250 (FDA 2014; MOHTT 2009:8).

When the first line drugs start to fail, after it has been determined that the patient is adherent to the medication, they are switched to second line combinations. In choosing first line NRTI backbones, it should be considered what should be reserved

for the second line NRTI backbone. In supporting this statement, the WHO (2010:53-57) also states that a new second line regimen has to involve drugs that retain activity against the patients' virus strain and should ideally include a minimum of three active drugs, one of them drawn from at least one new class, in order to increase the likelihood of treatment success and minimise the risk of cross resistance. The WHO (2010:53-57) recommends that the PI class is reserved for use in second line regimens in combination with two unused NRTIs. The continued use of 3TC or FTC in second line is recommended by some experts because it maintains the M184V mutation which confers a viral replication defect or may possess residual antiviral activity. Maintaining the M184V mutation is also thought to improve sensitisation of the virus to Zidovudine (AZT/ZDV), Stavidine (d4T) and TDF. AZT is thought to delay the emergence of K65R mutation which usually confers resistance to TDF. Thus, after failure of first line, combination of 3TC or FTC and AZT or TDF is thought to provide retained activity of AZT and TDF, while reducing viral fitness and replication. The clinical efficacy of this strategy has not been proven. Medecins Sans Frontieres (MSF) documented favourable outcomes observed in protease inhibitor-based second line regimens with at least one NRTI change (Pujades-Rodríguez et al 2008:1305-1312).

The second line drugs used in Trinidad are completely unused NRTIs and PIs. Patients who have previously used TDF and FTC with EFV or NVP are switched to AZT, 3TC and LPV/r. Those who used AZT and 3TC with EFV or NVP are switched to TDF, FTC and LPV/r. The majority of patients on second line HAART in Trinidad are on Truvada and LPV/r or Combivir and LPV/r. However there are several other PI-based regimens in use which are more appropriate in certain instances like the need to reduce pill burden, a regimen suitable for renal failure or liver toxicity. Some patients were also placed on PI-based regimens as first line drugs for certain situations such as during pregnancy, intolerance of NNRTIs, and continuation of PI as first line in patients already on PI as first line HAART, who have been transferred in from other health care facilities.

This research was a comparison of the PI-based regimens being used in Trinidad in order to determine and compare their efficacy. For the purpose of this research, the PI-based regimens in use in the San Fernando General Hospital (SFGH) HIV unit

were grouped in numbers as shown in table 1.2 (FDA 2014; Humphreys et al 2007; MOHTT 2009:9; Warnke, Barreto & Temesgen 2007:1570; Wools-Kaloustian et al 2006: 41-8).

Table 1.2: PI-based regimens in SFGH HIV clinic

NUMBER	REGIMEN
1	AZT +3TC+ LPV/r
2	TDF+FTC+LPV/r
3	TDF+FTC+ATZ/r
4	TDF+FTC+DRV/r
5	ddI + 3TC + LPV/r
6	AZT+3TC+SQV/r
7	ABC+3TC+LPV/r
8	TDF+3TC+IDV/r
9	AZT+3TC+IDV/r
10	TDF+FTC+AZT+LPV/r
11	TDF+FTC+SQV/r
12	ABC+3TC+ATZ/r
13	TDF+AZT+3TC+LPV/r
14	TDF+FTC+ABC+LPV/r
15	TDF+AZT+LPV/r

This study provides an opportunity to determine whether the PI-based regimens in use in Trinidad are of comparable efficacy. Determining the better combination will benefit patients and improve HIV care in Trinidad. The researcher recognised that new recommendations for the most ideal regimen to use for first or second line may each have their inherent disadvantages such as higher number of doses, intolerable side effects and unfavourable drug interactions. It thus leaves room for individualised patient care in which regimens are created based on patient presentation, history of ARV usage, previous side effects to ARVs as well as resistance test results, if available. The results of this research could contribute to the field of HIV/AIDS management in Trinidad, and possibly elsewhere in the world, provided that similar

studies have been conducted in other geographic locations. If it is found that all the regimens have the same efficacy, it may be advantageous for some patients who cannot use some ARVs due to side effects. Thus patients who develop M184V mutations could be placed on either regimen with confidence that they would do well.

1.3 RESEARCH PROBLEM

When first line ARVs fail in patients who adhere to the ART regimens, second line ARVs are used. The drugs recommended for use for second line in Trinidad are completely unused NRTIs and PIs. Patients who have previously used TDF and FTC with EFV or NVP are switched to AZT, 3TC and LPV/r. Those who used AZT and 3TC with EFV or NVP are switched to Truvada and LPV/r. Other second line combinations using other PIs are also in use. PI-based regimens are also being used for some patients as first line drugs because they could not tolerate NNRTIs, and also for pregnant women for the prevention of mother to child transmission of HIV (PMTCT). Studies comparing the efficacy of the PI-based HAART regimens in Trinidad could not be traced after an extensive search for published literature on the topic had been attempted.

Fifteen PI-based HAART regimens are being used in Trinidad but the treatment outcomes of these regimens have not been documented. Consequently it remains unknown whether there are differences between the effectiveness of the different PI-based HAART treatment regimens. This study attempted to provide information about these treatment outcomes. This information could be used when prescribing second line ARVs in Trinidad, to ensure that the best possible combinations of ARVs with the fewest side-effects are prescribed for specific patients.

1.4 AIM OF THE STUDY

This study attempted to compare the efficacy of different PI-based HAART regimens in Trinidad. (Although the title of the dissertation includes Tobago, permission could not be obtained to replicate the study in Tobago. Finances were also too limited to repeat the study in Tobago).

1.4.1 Research purpose

The purpose of the study was to compare the patients' treatment outcomes of the PI-based HAART regimens in Trinidad. Variables, impacting on ARV treatment outcomes, such as patients' treatment adherence levels, baseline as well as subsequent CD4 counts and VL levels, and other diseases (opportunistic infections and tuberculosis) were considered.

1.4.2 Research Objectives

The study attempted to determine whether the treatment outcomes of the PI-based HAART regimens in Trinidad were significantly different from each other.

The study aimed to compare the treatment outcomes of the PI-based HAART regimens in Trinidad by comparing the following aspects for patients on the regimens:

- baseline (when started on PI-based HAART regimens) CD4 and VL counts compared with these counts at 6, 12 and 18 months' treatment on PI-based HAART regimens
- HAART adherence levels as measured by regular clinical attendance
- WHO developmental stage of AIDS
- opportunistic infections
- side-effects of ARVs reported by patients
- deaths
- reasons why patients were put on a specific 2nd line HAART regimen
- patients' periods of failing on the 1st line HAART regimen before being changed to the PI-based HAART regimen.
- treatment outcomes of different PI-based regimens.

1.5 SIGNIFICANCE OF THE STUDY

This study could contribute to the body of literature comparing the efficacy of PI-based HAART regimens and may be significant in the HIV/AIDS treatment and care

guidelines for Trinidad. The study could provide evidence of the efficacy of the PI-based HAART regimens in Trinidad as well as evidence of the superiority of one PI-based HAART regimen over the other in Trinidad. If the efficacy of PI-based HAART regimens is less than the acceptable standard, it might mean there could be a need for more NRTIs for first or second line patients in Trinidad. A study such as this could identify a need for baseline resistance testing for patients before starting first or second line HAART.

The laboratory results will determine if there is a correlation between the VL count, CD4 count and clinical outcome of specific patients.

1.6 DEFINITIONS OF KEY TERMS

HIV: Human immunodeficiency virus is the virus that causes AIDS (HIV 2013).

AIDS: Acquired immune deficiency syndrome, caused by HIV, is a group of syndromes in humans caused by progressive failure of the immune system allowing life threatening opportunistic infections and cancer to thrive (Wikipedia 2013).

CD4: This is the receptor site of the T lymphocytes to which the HIV particle attaches itself to enter the cell to replicate itself. The T lymphocyte dies at the end of the HIV life cycle. A measure of CD4 levels is used to assess disease progression and the patient's response to treatment (Avert 2013).

WHO stages: Some symptoms of HIV/AIDS are diarrhoea, weight loss, oral thrush, skin rashes, tuberculosis, and malignancies, and patients are grouped based on clinical presentation into stages 1, 2, 3 and 4, in increasing order of progression of the disease, as was explicated in table 1.1 of this dissertation (WHO 2010: 27-28).

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Viral Load (V) is a measure of the level of the virus in HIV infected patients. It is measured at six months post initiation of HAART and six monthly thereafter. The HIV/AIDs treatment and care guidelines of Trinidad and Tobago regard levels above 1000 copies/ml as treatment failure (MOHTT 2009:9).

Anti-retroviral (**ARV)** drugs are drugs that reduce the level of HIV in the patient. Several different groups of ARVs are in use, each classified according to its mechanism of action.

Highly active anti-retroviral treatment (HAART) is a treatment paradigm using three or more antiretroviral drugs in combination. First line HAART is the first group of drugs used by HIV patients who have never used ARVs before. In Trinidad and Tobago, patients who have previously used TDF and FTC with EFV or NVP are switched to AZT, 3TC and LPV/r. Those who used AZT and 3TC with EFV or NVP are switched to Truvada and LPV/r (MOHTT 2009:9).

Immune reconstitution inflammatory syndrome (IRIS) usually occurs within the first six months of ART, in patients with very low CD4 counts at HAART initiation, and it is a paradoxical worsening of previously treated opportunistic infections (OIs) or the presentation of subclinical infections which are unmasked by the host's regained capacity to counteract and overcome an inflammatory response (French 2009:101).

2nd line HAART treatment outcomes pertain to the independent variables which in this study are the PI-based HAART regimens. The dependent variable refers to the treatment outcomes of the regimen measured by CD4, VL, and the WHO clinical stage of the patient.

2nd line HAART efficiency and inefficiency: A CD4 increase of at least 50cells/mm^3, after six months on second line HAART, will be regarded as indicating an acceptable efficacy, and a treatment success. Any drop in a patient's CD4 count to 50% of peak value, or any drop up to or below baseline pre-initiation of PI-based HAART after six months on a PI-based HAART regimen, will be regarded as being treatment failure. A CD4 count remaining persistently below 100cells/mm^3 after six months on PI-based HAART will also be regarded as being treatment failure (MOHTT 2009:9). Viral load (VL) above 1000 copies/ml, after six months on PI-based HAART, will be considered as being an ineffective HAART outcome (MOHTT 2009:9).

Clinical outcome will be assessed based on a change in disease progression evidenced by reported new opportunistic infections (OIs) or death, after being on PI-based HAART for at least six months. The appropriate staging will be recorded at six, 12 and 18 months on PI-based HAART for each patient. Progression to a more severe stage, while on PI-based HAART, will be regarded as failure once it has been determined that it is not IRIS, by a closer examination of the patients' record (MOHTT 2009:9).

1.7 FOUNDATIONS OF THE STUDY

No theoretical grounding will be used in this dissertation of limited scope, but the HIV/AIDS care and treatment guidelines of Trinidad and Tobago (MOHTT 2009) will be used as a basis for grounding this study. Some of the most important statements in this guideline which will be used as a guide for this study include:

- The ARVs used for second line in Trinidad are completely unused NRTIs and PIs. Patients who have previously used TDF and FTC with EFV or NVP are switched to AZT, 3TC and LPV/r. Those who used AZT and 3TC with EFV or NVP are switched to Truvada and LPV/r (MOHTT 2009:9).

- Definitions of failure on HAART will be accepted as outlined by the WHO definitions for clinical, immunological and virological failure in an adherent patient who has been on HAART at least six months (MOHTT 2009:9-12):

    - Clinical failure will be indicated by a new or a recurrent stage 4 condition.

    - Immunological failure will be indicated by a fall of a patient's CD4 count to or below baseline, or fall below 50% of on-treatment peak value or persistent CD4 values less than 100cells/mm^3.

    - Virological failure will be indicated by a plasma viral load greater than 1000 copies/ml and repeat viral load to confirm failure.

1.8 RESEARCH DESIGN AND METHOD

This was a quantitative non-experimental cross sectional retrospective study. It was a descriptive correlational study. Quantitative research adopts the positivist paradigm of research. This approach is appropriate for this study as it assumes that there is a reality to be proven. In this study, a correlation between the independent and dependent variables were examined to compare the HAART treatment outcomes (dependent variable) of patients on PI-based second line HAART regimens (independent variable) in use in Trinidad (independent variable) (Dawson 2009:15; Morroni & Myer 2007:77-78; Polit, Beck & Hungler 2001:169-186).

This study was a non-experimental study because the patients could not be randomly assigned to any category of second line HAART. The patients, whose medical files were examined, were already on second line HAART regimens before the study commenced. Cross-sectional designs are especially appropriate for describing the status of phenomena or relationships among phenomena at a fixed point. This study is retrospective because it captures events occurring in the past, as reflected in the medical records of patients on second line HAART, as the independent variables. The dependent variables in this study were the clinical, virological (VL) and immunological (CD4) outcomes which were recorded at fixed points of 6, 12 and 18 months after commencing second line HAART regimens. A descriptive correlational study describes relationships among variables. In this study, the major aim was to compare the treatment outcomes of the second line HAART regimens by assessing the clinical (WHO staging), virological (VL) and immunological (CD4) outcomes (Dawson 2009:15; Morroni & Myer 2007:77-78; Polit et al 2001:169-186).

The research methodology and design adopted throughout this study will be addressed in detail in chapter 3.

1.9 SCOPE OF THE STUDY

This study was only conducted on the records of patients who had been on second line HAART regimens for at least six uninterrupted months at the SFGH in Trinidad. The findings at the SFGH may not be generalisable to patients on second line HAART in Trinidad and Tobago who receive ARVs at other centers.

Patients on treatment for less than six months might encounter different challenges. Children and young persons (younger than 21 years of age) might experience different treatment outcomes from those experienced by older patients, but this fell beyond the scope of the current study.

Errors in recording information are possible. Information extracted from patients' records might have been inaccurately recorded. The checklists were carefully numbered and stapled together before starting with the data collection from any patient's record to prevent errors of transcription of information. There are several confounders that might affect the efficacy of HAART regimens. This study included a detailed literature review.

However, patients' records with possible confounding variables such as cancer, TB or major surgery will not be excluded from the study, but will be analysed statistically and these issues will be addressed. ARV resistance is not determined in all patients of SFGH before starting regimens, and the possibility of multidrug resistant HIV strains could affect the efficacy of second line HAART regimens.

However, the possibility of multidrug resistant HIV strains will be considered by the history of ARV drug usage as documented in the patients' medical records. The possibility exists of patients' false ARV use history, but the clinic attendances will be considered in this study and not the patients' self-reported adherence levels (Myer & Karim 2007:155-167).

1.10 STRUCTURE OF THE DISSERTATION

This dissertation has been written in five chapters as follows:

Chapter 1 discusses the background to the research problem, aim of the study, significance of the study, definition of terms used in the study specifically the independent and dependent variables, foundation of the study, and a brief description of the research design.

Chapter 2 reviews the literature on choosing second line HAART regimens, factors affecting efficacy of HAART regimens, and acceptable efficacy of second line HAART regimens. A model was designed by the researcher, based on the literature review, to contextualise the major aspects of this study.

Chapter 3 describes in detail the research method used in data collection, quality control, confidentiality control methods and analysis of the data.

Chapter 4 presents the data analysis and discussions.

Chapter 5 documents the interpretation of the research findings, provides answers to the research questions and recommendations for further research and modification of HAART regimens in Trinidad. This chapter also specifies the limitations of this study.

1.11 SUMMARY

It has been highlighted in this chapter that there is a need for a study such as this, comparing the second line regimens in use in Trinidad. Critical questions that may be answered by this study include reasons why patients were placed on either of the second line HAART regimens of Trinidad, their adherence levels to these regimens, side effects reported on second line medications and efficacy of the regimens. The purpose, objectives, significance, study methodology and the scope as well as the limitations of the study were discussed.

The next chapter will discuss the literature reviewed about the efficacy of second line HAART studies and methods used to carry out such studies. This provides information that will be compared with the results of this study.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

This chapter discusses the literature review, addressing what is known about the efficacy of HAART regimens and the methodology used in carrying out the study. An understanding of HIV biology is necessary to understand the mechanisms of action of ARVs, the combination strategies and the efficacy of different HAART regimens.

2.2 HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

In this section the biology and life cycle of the HIV will be discussed, followed by explaining how ARVs impact on the life cycle of the HIV.

2.2.1 Biology and life cycle of HIV

HIV is a microscopic organism, a virus, which destroys the body's inherent ability to fight disease, leading to AIDS (Avert 2013). There are several classifications of HIV variants, the most common in Trinidad being HIV 1, Subtype B (CHART 2001).

The virus has a circular shape. Its core ribonucleic acid (RNA) genetic material is covered by an envelope that has many small glycoprotein projections on its surface, the gp120 and gp41. These projections have an attraction to certain target cells with CD4 receptor sites (Avert 2013).

The core (or capsid) of the virus is usually bullet shaped. This core contains enzymes required for viral replication, reverse transcriptase, integrase and protease and the genetic material, which consists of two identical strands of RNA (Avert 2013).

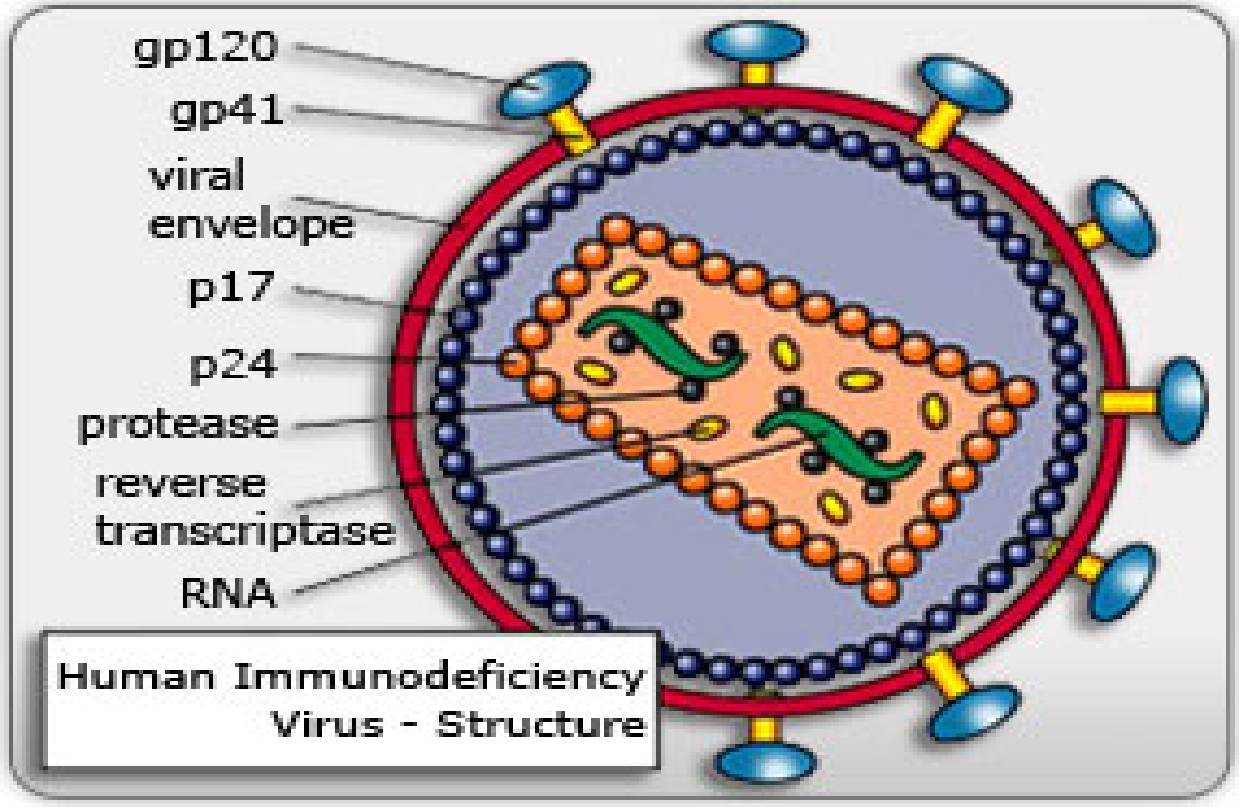

Figure 2.1 : HIV Structure

(Source: http://www.avert.org/hiv-virus.htm)

The HIV life cycle can be divided into a number of steps including succession, binding, fusion and entry, reverse transcription and integration, transcription and translation, then assembly, budding and maturation, which all take place in CD4 cells. The CD4 cell dies at the end of the cycle (Avert 2013). HIV principally affects CD4 T helper lymphocytes (TH cells). These TH cells are responsible for the initiation of nearly all immunological responses to pathogens, and following infection by HIV, there is attrition of the CD4 cell

population resulting in gradual and increasing failure of most aspects of immune function but particularly cell-mediated immunity, predisposing the body to OIs (Wilkins 2010). Specific ARVs aim to inhibit fusion and entry, such as reverse transcriptase, integrase and protease enzymes (Wilson, Naidoo, Bekker, Cotton & Maartens 2002:19).

2.2.2 Antiretroviral therapy (ART)

ARVs are supplied free of charge to patients in Trinidad. Who gets ARVs in Trinidad is determined by the HIV/AIDS treatment and care guidelines, based on the WHO's (2010:24) recommendations. The Trinidad HIV/AIDS treatment and care guidelines for adults and children recommend that all patients with CD4 counts of less than 350cells/mm^3 or with clinical staging from stage 3 upwards should commence ARVs (MOHTT 2009:5).

ARVs are grouped according to their mechanisms of action. The mechanism of action is best understood against the background knowledge of the life cycle of HIV (addressed in section 2.2.1). The currently approved groups of ARVs by the United States Food and Drug Administration (FDA) are the NRTIs, NNRTIs, PIs, fusion inhibitors, entry inhibitors, and integrase inhibitors (FDA 2013).

The NRTIs and NNRTIs inhibit the reverse transcriptase enzyme which is necessary for the HIV life cycle's developmental step of reverse transcription. In Trinidad, available NRTIs include d4T, 3TC, AZT, abacavir (ABC), didanosine (ddI), FTC and TDF. Truvada is a combination of TDF and FTC, and combivir is a combination of 3TC and AZT. The most notable class wide adverse effect of NRTIs is mitochondrial toxicity, which is responsible for the clinical syndromes of lactic acidosis with hepatic steatosis, peripheral neuropathy, and lipo-atrophy. Lamivudine, ABC, TDF and FTC are the NRTIs with low mitochondrial toxicity potential. The NNRTI group includes four approved drugs which are NVP, EFV, delavirdine, rilpivirine and etravirine. NVP and EFV are available in Trinidad. The most notable side effect associated with all NNRTIs is a rash which

usually occurs within the first six weeks of initiation of therapy and has been noted in up to 35% of patients receiving this treatment. NVP is also associated with hepatotoxicity, particularly in women with CD4 above 250cells/mm^3 and men with CD4 counts above 400 cells/mm^3 (MOHTT 2009:52).

PIs inhibit the protease enzyme responsible for the final cleavage of large viral precursor polypeptide chains into smaller, functional proteins, preventing maturation of the HIV virion (Wilson et al 2002). This results in the release of structurally disorganised and non-infectious viral particles. The FDA's currently approved PIs are fosamprenavir (FOS-APV), atazanavir (ATZ), darunavir (DRV), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), ritonavir (RTV/r), saquinavir (SQV), and tipranavir (TPV) (FDA 2013). Drug interactions are important considerations with the use of PIs. The PIs are substrates for the cytochrome P450 system in the liver and they also inhibit as well as induce this enzyme system to varying degrees, with RTV being the most potent inhibitor. This can cause a considerable number of interactions with drugs that are inducers, inhibitors, or substrates of this system. Three PIs (LPV, TPV and DRV) require co-administration with RTV to achieve effective serum concentrations. PIs available in Trinidad include ritonavir boosted lopinavir LPV/r, RTV, SQV, IDV, ATV and NFV (MOHTT 2009:52). The side effects of PIs include nausea, diarrhoea and vomiting. ATZ specifically causes skin rashes, and IDV could cause kidney stones (MOHTT 2009:52).

Entry Inhibitors and integrase inhibitors were not available for use in Trinidad (MOHTT 2009:52) when this study was conducted.

2.3 THE EFFICACY OF HAART REGIMENS

Antiretroviral regimens are modified for four reasons: toxicity, intolerance, treatment failure and evidence showing superiority of a different regimen. Switching from first-line to second line regimens is most frequently done in Trinidad in response to treatment

failure, and sometimes toxicity of prior regimens. Treatment failure can be assessed in three ways: clinically by disease progression and WHO staging, immunologically by CD4 trends over time and virologically by measuring the VL (MOHTT 2009:9).

Clinical failure is defined as new or recurrent WHO stage 4 conditions, and certain stage 3 conditions, including serious bacterial infections and tuberculosis. These conditions must be differentiated from IRIS, which normally occurs in the first six months following HAART and is a re-activation of a previously latent infection, or exacerbation of treated opportunistic infections (OIs) (MOHTT 2009:8-9). Immunological failure is defined in the Trinidad guidelines as well as the WHO guidelines, as a fall in CD4 counts to levels at or below pre therapy baseline levels or a 50% fall from the on-treatment peak value, or CD4 levels persistently lower than 100cells/mm^3 after 24 weeks on treatment, all in the absence of concomitant infection to cause transient CD4 cell decrease (MOHTT 2009:8-9). In Trinidad, CD4 levels are done at baseline, after three months on HAART, and at six months, and subsequently six monthly (MOHTT 2009:8-9). Virological failure is defined in the Trinidad guidelines as failure to achieve VL of less than 1000 copies/ml by 24 weeks in an adherent patient (MOHTT 2009:8-9). The WHO guidelines define virological failure as persistent plasma VL above 5000 copies/ml. VL levels must be correlated with clinical and immunological findings. The WHO recommends confirmation of treatment failure by viral load measurement. The WHO emphasises that switching of ARV regimens for treatment failure should only be considered when clinical and immunological criteria are used to confirm treatment failure (WHO 2010:48-52).

Before switching regimens due to treatment failure, non adherence, which is the most frequent cause of treatment failure, must be ruled out. Adherence counseling must be done and adherence readiness must be assured. When treatment failure is suspected, CD4 and VL are repeated after three months, and attempts should be made to identify and correct the cause(s) of treatment failure (MOHTT 2009:12).

Apart from non-adherence, there are several confounding variables that could affect the CD4 and VL levels as well as the clinical presentation of patients. According to Lab Tests Online (2012:1), CD4 counts can be influenced by analytical variations from the laboratory, seasonal and diurnal changes, with the lowest at 12.30pm and highest at 8.30pm. Gallant and Hoffman (2009) have elaborated that several variables can affect CD4 and VL levels in their article on CD4 count. Modest decreases in CD4 cell counts have been noted with some acute infections and with major surgery. Corticosteroid administration and interferon treatment cause severe decreases in CD4 cell counts. Medical conditions associated with low CD4 counts include Sjogren syndrome, sarcoidosis, radiation, atopic dermatitis, collagen-vascular disease, lymphoma, stem cell transplant recipients and idiopathic CD4 lymphopaenia. Acute changes are probably due to redistribution of leukocytes between the peripheral circulation and the marrow, spleen, and lymph nodes. Baseline CD4 also affects the increases in levels seen while on ART. Concurrent Human T-cell Leukaemia Virus Type 1 (HTLV-1) infection and splenectomy may lead to deceptively high CD4 levels. Gender, race, age in adults, risk category, psychological stress, physical stress and pregnancy have minimal effects on CD4 counts. Pregnancy leads to hemo-dilution and a small decline in CD4 count, but no decline in CD4%. Lab Tests Online (2012:1) state that due to the normal variability of CD4 cells, the number of CD4 cells can be compared to other types of lymphocytes. When compared to CD8 count, it is expressed as CD4/CD8 ratio and when compared to the total lymphocyte count, it is expressed as CD4%. Deciding if a CD4 level change is true and not a normal variation is made by comparing the CD4/CD8 ratios and CD4% which are relatively constant. Wilson et al (2002:47) stated that in HIV-negative individuals, the CD4 is slightly higher than the CD8 and the CD4/CD8 ratio is slightly above 1. When there is a true drop in CD4 levels, the CD4/CD8 ratio falls but in normal variation in HIV negative persons, the CD8 swings with CD4 levels and the ratio of CD4/CD8 is almost constant. This will be taken into consideration when deciding whether or not the patients in the study sample failed to respond to their regimens. Viral loads (VL) can be abnormally high following immunisation, acute illnesses and surgical procedures or hospitalisation (Gallant & Hoffman 2009). The clinical syndrome of IRIS

must be differentiated from new OIs, as IRIS occurs in patients with very low CD4 counts at HAART initiation, within the first six months of ART (MOHTT 2009:8-9). The first line regimen is given at least six months' time to detect immunological and virological improvements before considering switching to second line HAART. This research will identify whether or not confounding variables were present at the time of blood tests used to monitor the efficacy of second line regimens.

2.4 FACTORS AFFECTING THE EFFICACY OF HAART

The aim of ART is to make the amount of HIV in the body very low, preventing or reversing damage to the immune system, and preventing illness or restoring health to HIV-positive patients. Drug resistance is the inevitable consequence of incomplete suppression of HIV-1 replication, which depends on the efficacy of the regimen being used. Multiple factors influence the development of HIV drug resistance, including the biology of HIV, genetic barriers of ARVs to resistance, regimen potency, pharmacokinetics of ARVs, and medication adherence (Demeter, Bartlett & McGovern 2008).

● HIV Biology

Many drug resistant variants of HIV, which usually replicate less efficiently than drug-sensitive strains in the absence of specific drugs, are thought to pre-exist at low levels before drug therapy is initiated. A study in North Carolina, in the United States of America, revealed that there is high prevalence of transmitted resistance in newly diagnosed HIV-positive patients (Youmans, Tripathi, Albrecht, Gibson & Duffus 2011). A 2003 study in the Caribbean in Barbados uncovered a single viral strain that harboured resistance to ZDV, Zalcitabine (ddC) and ddI (CHART 2001). If virus replication is not fully suppressed by the ART regimen, these mutants can either cause overt virological failure, or, if replication in the presence of drugs persists, become more drug-resistant by the gradual accumulation of additional resistant mutations (Demeter et al 2008).

Sporadic observations have also shown changing patterns of transmitted drug resistant mutations in HIV infection even without selection pressure of ART (Reuter, Oette, Sichtig, Kaise, Balduin, Jensen & Häussinger 2011:188).

● Genetic barriers to resistance

HIV can develop high-level resistance to some drugs with only a single mutation, while other drugs require multiple mutations of the virus for the virus to become resistant to antiviral drugs' activities. The former drugs are referred to as having a ''low genetic barrier'' to resistance and the latter, a ''high genetic barrier''. Lamivudine, FTC, NVP and EFV have low genetic barriers. PIs have a high genetic barrier to resistance (Demeter et al 2008). Of treatment-experienced patients who failed a first line HAART regimen in South Africa, 80% had ARV-resistant virus which reflected the types of drugs used in the first- line regimens, and the viral subtypes (Marconi, Sunpath, Gordon, Koranteng-Apeagyei, Hampton, Carpenter, Giddy, Ross, Holst, Losina, Walker & Kuritzkes 2008:1590).

● Regimen potency

The potency of an individual drug or a combination of drugs is a crucial determinant of VL suppression. If the VL is not fully suppressed, continued virus replication in the presence of a drug can lead to the accumulation of mutations, leading to the development of virus resistance, even to drugs with a high genetic barrier to resistance. This research is about determining the most potent PI-based second line regimens in use in Trinidad, as well as the efficacy of each individual regimen (Demeter et al 2008; WHO 2010: 55-56).

● Pharmacokinetics

Sub-therapeutic levels of ARVs can be caused by low concentrations, adverse drug interactions as well as monotherapy. Low serum concentrations could pose problems for PIs, but could be offset by the use of pharmacokinetic ‘’boosting’’ with RTV. Use of certain medications, concurrently with ARVs, can reduce serum concentrations of the drug such as the use of Rifampicin (an anti-TB medication) which is contra-indicated for combinations with both NVP and LPV/r because it reduces the serum concentration of these drugs by 20-58% and 75% respectively. A thorough understanding of these interactions is necessary for clinicians who prescribe ARVs (WHO 2010:46).

● Medication adherence

It has been proposed that the relationship between adherence and drug resistance is complex and influenced by drug potency and pharmacokinetics (WHO 2010:70). A study by Alcorn and Thaczuk (2008) in British Columbia showed that adherence levels exceeding 95% are necessary to maximise the benefits of ART. In a study in China, patients with detected viraemias had increasing prevalence of NRTI and NNRTI-resistant mutations within months of being on therapy (24.3% at 3-6 months, 57.1% at 9-12 months and 63.3% at 20-24 months) which were attributed to low levels of adherence to ARVs (Luo, Liu, Zhuang, Lui, Su, Yang, Tien, Zhang, Gui & Chen 2009).

Based on the literature review and on the researcher’s experience of treating PLWA/H, a model was designed to portray the factors affecting the efficacy of second line HAART regimens and the possible outcomes of second line HAART uninterrupted therapy for at least six months.

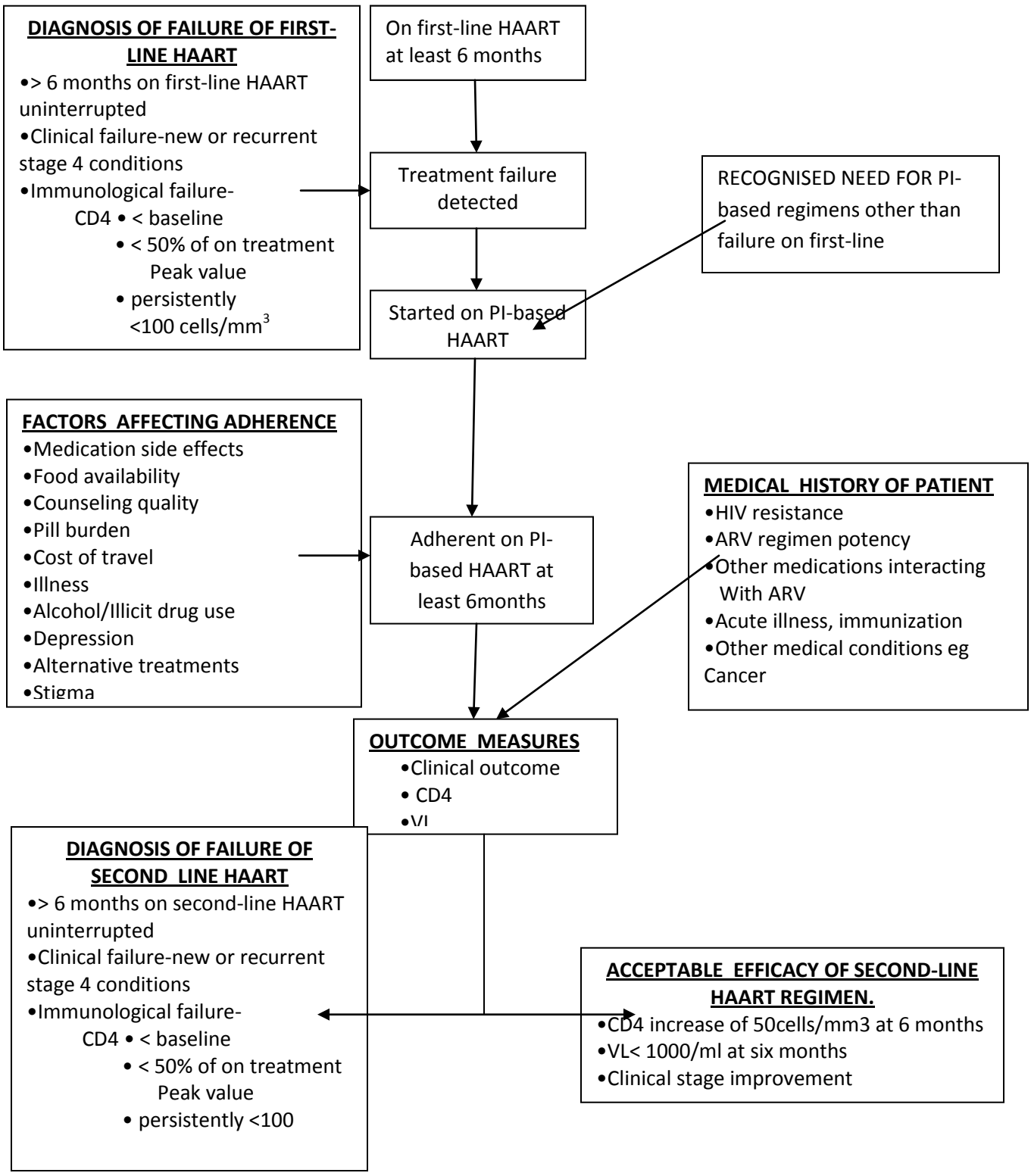

Figure 2.2: Conceptual model of factors affecting the efficacy of second line HAART regimens and possible outcomes of second line HAART uninterrupted therapy for at least six months.

2.5 COMPARING THE EFFICACY OF DIFFERENT HAART REGIMENS

In choosing NRTI backbones, clinicians should consider what should be reserved for the second line NRTI backbone. Knowledge of the resistance patterns developed in response to first line ARVs is employed in choosing regimens to use as second line ART regimens. In supporting this statement, the WHO (2010:53-57) also states that a new second line regimen has to involve drugs that retain their activity against the patients' virus strain and should ideally include a minimum of three active drugs, one of them from at least one new class, in order to increase the likelihood of treatment success and minimise the risk of cross resistance. The WHO recommends that the PI class should be reserved for use in the second line regimen in combination with two unused NRTIs. Medecins Sans Frontieres (MSF) documented favourable outcomes in protease inhibitor-based second line regimens with at least one NRTI change (Pujades-Rodríguez et al 2008:1305-1312). The PI of choice in Trinidad is the RTV boosted LPV, LPV/r. Patients who have previously used TDF/FTC/EFV or NVP are switched to AZT/3TC/LPV/r. Those who used AZT/ 3TC/EFV or NVP are switched to TDF/FTC/LPV/r (MOHTT 2009:10).

The WHO (2010:53) states that few studies were identified in a systematic review conducted with the objective of assessing the optimum second line ART regimen in patients failing first line therapy, in resource limited settings.

There is cross resistance between 3TC and FTC. The WHO (2012:11) stated that these two drugs are similar in activity, and can be used interchangeably. Studies proving the efficacy of using either drug after the other had failed in a previous regimen could not be identified. M184V mutation is developed against 3TC and FTC. The continued use of 3TC or FTC in second line ART regimens is recommended by some experts because they maintain the M184V mutation which confers a viral replication defect (Wei, Liang, Götte & Wainberg 2002:2392) or may possess residual antiviral activity (Highleyman 2009). Maintaining the M184V mutation is also thought to improve sensitisation of the

virus to AZT, d4T and TDF. A study in British Columbia, Canada, by Hull et al demonstrated that amongst individuals with documented M184V mutations, with or without additional NNRTI resistance, standard three - drug boosted PI-based regimens containing 3TC “appeared equally effective’’ at achieving virological suppression compared with more intensive multi-drug combinations or 3TC-sparing regimens (Highleyman 2009). Patients taking 3TC or FTC plus another NRTI and a PI were as likely to achieve undetectable viral load as those with completely unused NRTIs (Pujades-Rodríguez et al 2008:1305-1312). The patients in the present study were presumed to have developed M184V mutation to 3TC or FTC on the first line regimens in use in Trinidad (MOHTT 2009: 9).

In Guyana, the preferred first line regimen is TDF/FTC/EVF. There are two second line regimens in use in Guyana, 2a and 2b which both use TDF/FTC as the NRTI backbones, the same as is used in the first line regimens, with PI, LPV/r. The 2b regimen has AZT added to the NRTI backbone. After failure of the first line ART regimen containing 3TC or FTC, combinations of 3TC or FTC and AZT with TDF are thought to provide retained activity of AZT and TDF, while reducing viral fitness and replication (MOHG 2010/2011). There was no documented study done in Guyana to prove the clinical efficacy of this strategy. In a study done in India using the same second-line HAART regimens as in Guyana, there was no significant difference in the efficacy of the two regimens. However, all the patients in the study in India used AZT and 3TC in their first line regimen with EFV or NVP (Guha, Bhandari, Pain, Saha, Goswami & Ray 2011). If there was any significant difference, it might be relevant in choosing second-line regimens in Trinidad. A few patients in Trinidad use a similar regimen as the 2b regimen in Guyana when the prior ARV history suggested this to be the appropriate combination.

All NRTI have in common the K65R mutation developing when regimens fail. AZT is thought to delay the emergence of K65R mutation which usually confers resistance to TDF. Thymidine analogue mutations (TAMs) are developed to AZT and d4T. In vitro

studies demonstrate that K65R and TAMs are rarely detected in the same plasma sample. Such studies demonstrate that the introduction of K65R into recombinant viruses containing TAMs reduced AZT resistance from over 50-fold to less than threefold. In contrast, the presence of TAMs decreases the likelihood of K65R selection. Findings such as this may imply that the use of AZT in combination with 3TC and an NNRTI, as a first line regimen, may preserve TDF for use in second-line regimens, when it would be a completely unused ARV and development of K65R is prevented by TAMS which have occurred in the first line regimen, to AZT. Then AZT resistance due to the development of TAMs would be reduced significantly by the introduction of TDF and continuance of FTC. The function of FTC, as antiviral in this case, would be negligible because of the high level of resistance conferred by M184V to FTC and 3TC, but also advantageous in increasing susceptibility to AZT and TDF. Using AZT in the first ART regimen might prolong the first line regimen because it has a high genetic barrier to resistance, and at least three TAMs are required before all virologic activity of AZT is completely lost. Noteworthy is the potential for AZT to cause anaemia.

The TDF/FTC combination has the advantage of minimal side effects of the combination, and a once daily dosing regimen, making the patients' lives easier and probably enhancing ART adherence levels. An alternative would be to continue using d4T/3TC/NNRTI as first line regimen, then switch to TDF/AZT/FTCPI as second-line, and in this way, TDF and AZT would be completely new drugs reserved for second-line. But d4T causes unfavourable side-effects of dyslipidaemia, lactic acidosis and/or pancreatitis and peripheral neuropathy (Bartlett, Hirsch & McGovern 2008; Cohen, Gallant, Bartlett & McGovern 2008).

In a study in Cambodia, a high efficacy of LPV/r second-line ARV regimen was achieved (Ferradini, Ouk, Segeral, Nouhin, Dulioust, Hak, Fournier, Lerolle, Ngin, Mean, Delfraissy & Nerrienet 2011). However, a combined efficacy of four different regimens was used in that study which compared regimens of didanosine (ddI)/3TC/LPV/r (65.7%), ddI/TDF/LPV/r (10.0%), ddI/AZT/LPV/r (8.6%) and TDF/3TC/LPV/r (7.1%).

Another study in South Africa showed high rates of survival, immune reconstitution and virologic suppression in patients on second-line HAART using ddI/AZT/LPV/r (Fox, Ive, Long, Maskew & Sanne 2010).

2.6 METHODOLOGIES USED IN STUDIES THAT COMPARED HAART REGIMENS

Several methods have been used by previous researchers to evaluate second-line HAART efficacy including observational cohort and case control methods, randomised controlled trials, systematic reviews and meta-analysis. The WHO used a standard Cochrane review method, including several studies that adopted these methods, to carry out a meta-analysis to gather data before making its current recommendations in 2010. Ferradini et al (2011:14) studied second-line regimen efficacy in Cambodia retrospectively by analysing their immune-virological data at a fixed point. In the study in India by Guha et al (2011), a retrospective patients' chart review was done. This is the same method that was used in the current study.

2.7 CONCLUSION

There is an urgent need for research to determine the efficacy of second-line HAART regimens currently recommended by the WHO. Clinicians could use this information for choosing future regimens to enhance their patients' treatment outcomes and to make cost-effective clinical decisions.

In this study, PI containing second-line regimens AZT/3TC/LPV/r and TDF/FTC/LPV/r were the major HAART regimens being studied. However, some other regimens containing PIs are also being used at the center. The data were also extracted for these regimens and analysed. The next chapter will present the research method and design adopted by this study.

CHAPTER 3

RESEARCH DESIGN AND METHOD

3.1 INTRODUCTION

In this chapter, the methodology that was used in the study is explained. The research design and method, sampling, data collection and analysis and ethical considerations are addressed in this chapter. It was a quantitative study and the data were extracted from the records of patients by the researcher using self-designed checklists.

3.2 RESEARCH DESIGN

A research design is an overall plan for addressing a research question and it includes a description of what has been done to enhance the integrity of the study. This was a quantitative non-experimental cross sectional retrospective survey. It was a descriptive correlational study, comparing the treatment outcomes of patients on HAART regimens containing PIs (second line ART).

This study was a non-experimental study because the patients could not be randomly assigned to any category of HAART. The patients, whose medical files were examined, were already on PI-based HAART regimens before the study commenced. Cross-sectional designs are especially appropriate for describing the status of phenomena or relationships among phenomena at a fixed point (Polit et al 2001:169-186, 470). This study is retrospective because it captures events occurring in the past, as reflected in the medical records of patients on PI-based HAART regimens in Trinidad, as the independent variables. The dependent variables in this study were the clinical

(WHO staging), virological (VL) and immunological (CD4) outcomes which were recorded at fixed points of 6, 12 and 18 months after commencing PI-based HAART regimens. A descriptive correlational study describes relationships among variables. In this research, the major aim was to compare the treatment outcomes of the PI-based HAART regimens by the clinical (WHO staging), virological (VL) and immunological (CD4) outcomes (Dawson 2009:15; Morroni & Myer 2007:77-78).

3.3 RESEARCH METHOD

The research method indicates the steps, procedures and strategies for gathering and analysing data in a research investigation. The population, sampling method and sample will be described in this section of the dissertation, as well as the research instrument and the data gathering process (Polit et al 2001:465).

3.3.1 Population

A study population is defined as any universe of subjects, cases, units or observations (Stommel & Wills 2004:441). A population comprises "… all elements, including individuals, objects, events, or substances that meet the sample criteria for inclusion in a study, sometimes referred to as a target population" (Burns & Grove 2009:714). At the SFGH HIV clinic, 59 patients aged 21 and older had been on PI-based HAART regimens for at least six months by 31 August 2013 (SFGH records 2013). All 59 patients, on PI-based HAART for at least six months by 31 August 2013, and who were 21 years old or older, comprised the target population for this study.

3.3.2 Sampling method and sample

Sampling is the process by which a predetermined number of observations or persons are selected from a larger population to participate in a study. "Sampling theory determines mathematically the most effective way to acquire a sample that would accurately reflect the population under study. The key concepts of sampling theory are

population, elements, sampling criteria, representativeness, sampling errors, randomisation, sampling frame and sampling plan" (Burns & Grove 2009:343). The sample is representative of the population if a random sample has been selected. In random sampling, "… each member of the population has a probability greater than zero of being selected for a study" (Burns & Grove 2001:40).

In this study, the 2013 records of the SFGH HIV clinic did not indicate which patients had been on PI-based HAART regimens for at least six months by 31 August 2013, and who were 21 years old or older. A manual count of all the records was done and the patients were categorised into four groups; not on ART, on NNRTI based ART, on PI-based ART and salvage regimens. The patients in each group were further sub-classified into active and inactive subgroups. Inactive patients were those not on HAART who had not been to the clinic for six months or longer; those on HAART who did not have ARVs to cover the period up to three months after their last prescribed medications should have been finished. Active patients were those who kept to their clinic appointments and whose records of prescribed ART were sufficient to cover the periods of absence from the clinics. The inclusion criteria were active patients over the age of 21 on PI-based regimens at least six months at the time of data collection. Data were extracted from all patients' records that fit into the criteria. A total of 59 patients were included in the study during data collection, but during analysis, due to missing data, only 35 patients' data were included. The exclusion criteria stipulated that patients who had no baseline CD4 and no CD4 value at six months could not be included in the current study.

3.3.2.1 Data collection approach and method

Data were collected using a self designed checklist (Annexure 1) to extract data from the records of patients included in this research.

3.3.2.2 Development and testing of the data collection instrument

The data collection instruments were designed after the literature review of studies, which identified several factors that affect HAART efficacy including confounders. A pre-test was done by using the checklist to extract data from ten records by two different persons and then the data were extracted again from the same ten patients' records by the researcher, and the information gathered by two people was compared to identify any discrepancies. The different records were identical and no discrepancies were detected.

3.3.2.3 Characteristics of the data collection instruments

The quality of the data collection instrument was assured by assessing the reliability and validity of the self designed checklist.

- **Reliability**

Three aspects of reliability are of interest to researchers collecting quantitative data: stability, internal consistency, and equivalence.

Stability is a measure of the extent to which the same scores are obtained when the instrument is used with the same sample on separate occasions. This is derived through test-retest reliability procedures. The checklist was pretested as elaborated in section 3.3.2.3.The result for the two sets of 10 records was compared (Polit et al 2001: 303-312) and no discrepancies were found.

An instrument is said to have internal consistency to the extent that all its subparts measure the same characteristic. This was applied in creating the checklist by grouping the questions under five sections: demographic and medical information, HAART history, counselling and adherence information, second-line treatment history and side-effects. The Cronbach alpha coefficient could not be calculated for this study because

the large number of missing values from the patients' records would have produced negative values (Polit et al 2001: 303-312).

Equivalence determines the consistency or equivalence of the instruments by different observers. This did not apply to this research (Polit et al 2001: 303-312).

- **Validity**

Validity of measuring instruments is the degree to which an instrument measures what it is supposed to be measuring. There are several aspects of validity of instruments: face validity, content validity, criterion-related validity, and construct validity.

Content validity is concerned with the adequacy of coverage of the content area being measured. Content validity is based on the fact that the researcher is an experienced HIV clinician who has done a detailed literature review before creating the checklist. Four other doctors working in the HAART field determined the relevance of every item in the checklist for identifying differences in the outcomes of the two groups of patients (Polit et al 2001: 303-312; (Validity in Research Design 2009).

Construct validity refers to the testing of relationships predicted on the basis of theoretical considerations. In this research, patients who are adherent to second line HAART are expected to have increased CD4 and reduced VL and an improvement in their clinical staging of the disease (Validity in Research Design 2009).

3.3.2.4 Data collection process

Information was transcribed from patients' records using checklists. A list of patients' records included in this study was compiled, indicating each patient's file number and the corresponding completed checklist's number.

3.3.2.5 Ethical considerations related to data collection

The list comprising each patient's file number and checklist number was locked up in the office of the head of department for HIV/AIDS care and only the researcher had access to this list, in case the healthcare authorities or research authorities should require audits of the recorded data. This list would be destroyed subsequent to the acceptance of the research report. The completed checklists were anonymous, only indicating each respondent's checklist number (Polit et al 2001:75-83).

3.3.3 Data analysis

A statistician assisted with the data analysis and interpretation. Descriptive statistics were used for describing the respondents' demographic characteristics and to measure associations using SPSS version 20. Associations between CD4 change percent and several variables were determined using chi-squares. The p-value was set at <0.05 for statistical significance (Joubert 2007:141-151).

3.4 INTERNAL AND EXTERNAL VALIDITY OF THE STUDY

The adequacy of a research design could be evaluated by an assessment of its internal and external validity.

- **Internal validity**

Internal validity refers to the extent to which it is possible to make an inference that the independent variable (PI-based HAART regimen) is truly influencing the dependent variables (CD4, VL, side effects, OIs). Threats to internal validity could be posed by the patient's history, selection, maturation or mortality (Validity in Research Design 2009).

The history threat is the occurrence of events concurrently with the independent variable that can affect the dependent variable. Several variables affect the efficacy of HAART, apart from the regimen potency, including adherence to HAART medications,

baseline CD4 and VL, presence of OIs, acute illnesses, major surgery and interactions with other medications. In records where there were unacceptable levels of CD4 or VL counts, a thorough re-examination of the records was done to determine whether any confounding variables were present at the time of the laboratory analysis. Any other factors (such as suffering from cancer or tuberculosis, using corticosteroids or interferon, major surgery and records of counseling sessions) identified in the patients' records that might influence the HAART outcomes, were recorded on the checklist and indicated in the presentation and discussion of the research findings (Polit et al 2001:193).

Inclusion and exclusion criteria are a means of establishing precision in a study. Inclusion criteria are the criteria for including a patient in a study. Exclusion criteria are the criteria for excluding patients from the study. The inclusion criteria for the PI-based HAART regimens patients' records are patients aged at least 21, on a PI-based HAART regimen for at least six uninterrupted months, with baseline and 6 months after treatment CD4 and VL results recorded in their files. The patients' records were excluded if they had not been on PI-based HAART for at least six uninterrupted months or if they were younger than 21 years of age, or if they did not have baseline CD4 and VL results or if these results were not recorded 6 months after they had commenced PI-based HAART.

A selection threat encompasses biases resulting from pre-existing differences between groups, and might arise if respondents are not assigned randomly to groups. CD4 cell recovery has been related to the age of patients, younger patients are known to have a faster CD4 recovery. CD4 cell recovery is also related to basal CD4 cell counts. During the analysis of data, patients' CD4 cell counts change percentages were stratified by age and baseline CD4 quartiles for the different groups of PI-based HAART regimen patients (Myer & Karim 2007; Polit et al 2001:187-195).

The threat of maturation arises from processes occurring within the subjects as a result of time rather than from the independent variable. In HIV-positive patients, without HAART, CD4 drops over time, while the VL rises. It is expected that the opposite will be the case in the research population on second line HAART regimens as long as they are adherent to their medications. Having a recorded trend of increasing CD4 and reducing VL in the patients' files, could indicate that they were adherent to HAART. Falsely elevated CD4 counts, as seen in HTLV-1could not be controlled because the HTLV-1 serology of the patients were analysed at the participating healthcare facility but it was not exactly clear at what point in their care they had that investigation done. Splenectomies, which can increase patients' CD4 counts falsely, would be recorded on the checklists (Polit et al 2001:187-195) if recorded on the patients' files.

Threats of mortality arise from differential attrition rates from the different groups of patients on different PI-based HAART regimens. Patients' records were used, and only those who had been on PI-based HAART for at least six uninterrupted months were studied. Consequently, attrition and mortality were not expected to impact on this study. However, the availability and accessibility of patients' records, as well as the completeness and accuracy of these records, might have influenced the data collection procedure in unpredictable ways (Polit et al 2001:187-195).

- **External validity**

External validity refers to the extent to which the research results can be generalised beyond the sample. The records of all patients at the centre who fit the inclusion criteria were included in the study. The results of this study will only be relevant for patients who had been on PI-based HAART regimens in Trinidad for at least six uninterrupted months by 31 August 2013 (Polit et al 2001:187-195).

Possible confounding variables that might impact on patients' VL and CD4 counts were identified and discussed, such as TB, cancer, major surgery, splenectomy, recent immunisations and pregnancy.

3.4 ETHICAL CONSIDERATIONS

The research proposal was submitted to the Higher Degrees Committee of the Department of Health Studies, University of South Africa. After the proposal had been revised, it was accepted by this committee and an ethical clearance letter was issued (see Annexure 2).

Permission was obtained from the ethics committee of the SFGH before carrying out this research (see Annexure 3). The manager of the participating health facilities were informed about the study and about the permission obtained to collect data. Each manager then granted permission for the researcher to collect data from the patients' records. No human data sources were used in this research. Only medical records of patients aged 21 and older were used to collect data by means of completing self-designed checklists. There were no risks for the patients.

3.5 SUMMARY

The method used to design the study, sampling, data collection and analysis and the existence of threats to the validity of the study, as well as several confounders have been investigated in this chapter.

The next chapter will present the analysis and discussion of the data obtained during the analysis of the information transcribed from the patients' records.

CHAPTER 4

ANALYSIS, PRESENTATION AND DESCRIPTION OF RESEARCH FINDINGS

4.1 INTRODUCTION

This chapter presents and discusses the findings of this study. Where relevant, these results will be compared with those of other studies.

4.2 DATA MANAGEMENT AND ANALYSIS

Checklists were completed from the records of patients attending the HIV clinic of the SFGH. As many as 15 PI-based regimens were in use in the SFGH (see table 1.2). There was no immediately available method of identifying patients who fit the inclusion criteria of this study. A manual count of medical records was done and a total of 1 212 medical records were available. The patients' records were classified into four groups, namely those:

- not on ART (n=289; 23.8%)
- on NNRTI-based ART (n=669; 55.1%)
- on PI-based ART (n=245; 20.2%) and
- on salvage regimens (n=9; 0.7%).

Each category was classified into two groups: active or inactive. Inactive patients were those not on HAART or who had not been to the clinic during the preceding six months. For those on HAART, inactive patients did not have ARVs to cover the period up to three months after their last prescribed medications should have been finished. Active patients were those who kept their clinic appointments and whose records of prescribed ARVs were sufficient to cover the periods of absence from the clinics.

A total of 164 patients were active on PI-based regimens and 15 different PI-based regimens were in use, as indicated in table 1.2. The PI-based regimen in current use was recorded as each patient's current regimen and the date when that regimen was started was taken as the baseline for that patient. The CD4 and VL, taken just before the start of the current PI-based regimen, were taken as baseline values. There were a total of 59 patients on their current PI-based regimens for at least six months, who were at least 21years of age. However, during data analysis, due to missing data, only 35 patients' data were included (N=35) and they comprised the population of this study.

All 35 patients had previously used ARVs before their current PI-based regimens. Some patients were switched to the current PI-based regimens after using NNRTI-based regimens containing two NRTIs and one NNRTI. Some had used both NNRTI-based and PI-based regimens before starting the current regimen. Patients were switched to the current PI-based regimens for reasons such as failure of prior first line NNRTI-based regimens, toxicity to previous NNRTI-based regimens or PI-based regimens, to reduce pill burden of prior PI-based regimens, pregnancy and tuberculosis. Some were transferred from other health care facilities, when they were already on their PI-based regimens and for uncertain reasons (as stated on the patients' files). Baseline and six months on treatment CD4 and VL values were extracted. Only the CD4 counts at six months were used because that was the month with the least missing values for all patients who fit the inclusion criteria. Patients' records without baseline CD4 and without CD4 values at six months were excluded from this study.

The CD4 change percent was recorded for all patients and the relationship with the independent variables were inferred by using SPSS version 20.The CD4 change percent was computed, using SPSS, by the following equation:

$$\frac{\text{6months CD4-Baseline CD4}}{\text{Baseline CD4}} \times 100$$

CD4 has a normal variability (Lab Tests Online 2012:1) and a wide range of normal values, and the CD4/CD8 ratio might have been more appropriate to compare CD4 levels between different records. However, this was impossible during the current study because the patients' CD8 values were not measured at this center. There were CD3 values available for a handful of patients, and this was not used in the analysis because it was not recorded for all the patients (Wilson et al 2002:47). Due to its wide variability, the baseline CD4 values were grouped into quadrants:

- 1 (CD4 <50cells/mm^3)
- 2 (CD4= 50-<100 cells/mm^3)
- 3 (CD4=100-<200 cells/mm^3), and
- 4 (CD4= 200-<300 cells/mm^3).

A fifth group: 5 (CD4 >300 cells/mm^3) was included because some patients might have attained high and normalised CD4 counts and maintained these counts without showing any increased CD4 counts during the time that this study was conducted.

All the independent variables, identified during the literature review and included in the checklist, could not be addressed from the data available in the HIV clinic's files. The independent variables considered for their influence on CD4 change percent in the current research were gender, age, HAART regimen, prior ARVs used, change of all NRTI or not, prior non-adherence to PIs, failing on the previous regimen just before switching to the current PI-based regimen, period without ARVs before starting on current PI-based regimen, type of regimens previously failed, previous switches between PIs, and baseline CD4 quadrant. Weights and staging of HIV disease were not analysed because these aspects were not recorded for every patient at each clinic visit.

HIV-positive patients not on HAART record CD4 drops over time, while their VL rises. It was expected that the opposite would be the case in the research population on second-line HAART regimens as long as they were adherent to their medications. Having a trend of increasing CD4 and reduced VL counts in the patients could indicate

that they were adherent to HAART. Possible confounding variables that might impact on patients' VL and CD4 counts were identified during the literature review, such as TB, cancer, major surgery, splenectomy, recent immunisations and pregnancy. Any of these variables in a patient's files were recorded on the patient's checklist (Avert 2011; MOHTT 2009:9).

Falsely elevated CD4 counts, as seen in HTLV-1, could not be controlled because the HTLV-1 serology of the patients were analysed at the participating healthcare facility but it was not exactly clear at what point in their care that investigation was done. Some patients were given appointments to get the tests done but they did not go for the tests on the appointed dates. Splenectomies, which could increase patients' CD4 counts falsely, were not recorded on any patient's file.

Medication adherence was assumed to be good for all the patients included in this research, based on the dates of their clinic attendances. Patients, who missed their clinic dates for refills of ARVs and who did not have ARVs to cover the period of non-attendance at the clinic, were assumed to be non-adherent and were excluded from the study.

There were occasionally recorded statements by the doctors of a few pills missed per month as verbalised by the patients, but this was not used to analyse adherence levels as the patients might not have provided accurate information and these records were infrequent.

4.3 RESEARCH RESULTS

Descriptive statistics were used for describing the respondents' demographic characteristics and to measure associations using SPSS version 20. Several variables were tested and compared for their effect on the CD4 change percent. A significance level indicates how likely it is that a result is due to chance. The most common level, 95% significance level means the finding concerned is 95% likely to be true.

Most statistical packages would show a 95% significance level as 0.05, also known as the p value meaning it has 5% chance of not being true. In this research, the p-value was set at <0.05 for statistical significance. Any p value in this research found to be greater than 0.05 implies that the result has a higher than 5% chance of not being true, and the finding was regarded as insignificant. Variables which were found to significantly affect CD4 change percent were tested for correlations to rule out confounders.

Patients were started on their current PI-based regimens for reasons including failure on first line NNRTI-based regimens (68.5%; n=24), toxicity of NNRTI (14.2%; n=5), or prior PI-based regimens (n=3; 8.6%), to reduce pill burden of prior PI-based regimens (2.9%; n=3), pregnancy (5.7%; n=2), tuberculosis treatment (5.7%; n=2), transferred from other health care facilities already on PIs (5.7%; n=2) and in one patient's file, the reason stated was "uncertainty". Some of these patients were started on their current PI-based regimens for more than one of the recorded reasons.

Out of the eight patients who had used other PI-based regimens before the current one two (25.0%) were switched for prior PI non availability; two (25.0%) for prior PI non adherence, one (12.5%) for having commenced TB treatment, three (37.5%) for side effects of prior PI-based regimens, and two (25.0%) at the patient's request. Some patients switched their regimens for more than one reason, explaining why the percentages do not add up to 100%.

Variables which were tested for their influence on CD4 and VL include gender, age, HAART regimen, prior ARVs used, change of all NRTIs or not, prior non-adherence to PIs, failing on the previous regimen just before switching to the current PI-based regimen, period without ART before starting on current PI-based regimen, type of regimens previously failed, previous switches between PIs, and baseline CD4 quadrant.

4.3.1 The association of gender and baseline CD4 and CD4 change percent on PI-based regimens

Table 4.1: Baseline CD4 quadrant and gender (N=35)

Base CD4 quadrant	n	Gender	SD	df	p
1: 1<50	4	1.25	.500		
2: 50<100	3	1.67	.577		
3:100<200	9	1.22	.441		
4: 200<300	5	1.60	.548		
55>300	14	1.36	.497		
Total	35	1.37	.490	34	.537

Of the 35 patients included in the analysis, there were 13 (37.1%) females and 22 (62.9%) males. In this study, the baseline CD4 was compared for both genders.
The baseline CD4 quadrant was not significantly affected by gender (P=0.537) (see table 4.1). Therefore males and females did not have statistically significant different baseline CD4 counts in this study.

Kumarasamy, Venkatesh, and Mayer (2008:1471) stated that there were higher CD4 counts in ARV naïve HAART treated women in India compared to males, before and after one year on HAART. These authors attributed this phenomenon to differences in physiological, immunological and clinical gender differences. However, in that study, NRTI-based regimens were used in ARV naïve patients. Thorsteinsson, Ladelund, Jensen-Fangel, Johansen, Katzenstein, Pedersen, Storgaard, Obel and Lebech (2012:293) demonstrated a higher baseline CD4 and lower baseline VL in women than in men before starting HAART, but immunological and virological responses were not significantly different for the two genders. In that study, both NNRTI-based and PI-based regimens were used.

It was also revealed in a study in Senegal on HIV negative persons that men maintained a lower CD4 count than women (p<0.01) (Mair, Hawes, Agne, Sow, N'doye, Manhart, Gottlieb & Kiviat 2008:432-440). The findings of these studies appear to contradict the findings of the current research. However, the patients in the current research were not ARV naïve and the baseline CD4 was the CD4 taken just before the current PI-based regimen started, not before they commenced taking ARVs for the very first time in their lives. Some of the current study's 35 respondents were on failing regimens (60.0%; n=21) while others were on successful regimens (40.0%; n=14) before commencing with their current PI-based regimens.

Table 4.2: CD4 change percent and gender (N=35)

GENDER	n	Mean	SD	df	p
1 (males)	22	67.14	108.035		
2 (females)	13	53.31	86.848		
Total	35	62.00	99.584	34	.698

Response to therapy was also analysed for the patients on PI-based regimens (N=35) by comparing CD4 change percent for males (62.8%; n=22) and females (37.1%; n=13), and there was no statistically significant difference (p>0.698) (see table 4.2). Therefore in this research, the immunological responses to the PI-based regimens were not affected by gender. There are conflicting literature reports on the effect of gender on CD4 increased counts while on HAART. Kumarasamy et al (2008:1) stated that there was higher CD4 after one year on HAART in females than males. A study comparing treatment outcomes of NNRTI-based regimens showed that being female was associated with greater CD4 increase on HAART (Gandhi, Spritzler, Chan, Asmuth, Rodriguez, Merigan, Hirsch, Shafer, Robbins & Pollard 2006:426-34). A study in Uganda (Sempa, Kiragga, Castelnuovo, Kamya & Manabe 2013:e73190) revealed that women who sustained virological suppression achieved a better sustained immunologic recovery than men. These studies' findings seem to contradict the findings of the current study. However, the findings of a study by Smith, Sabin, Youle, Kinloch-de Loes, Lampe, Madge, Cropley, Johnson and Philips (2004:1860-1868), attempting to identify the factors influencing increases in CD4 cell counts in HIV patients on HAART, were

similar to the current study's findings in that the CD4 cell increase on HAART was not affected by gender. Thorsteinsson et al (2012:293) also demonstrated that immunological and virological responses were not significantly different for the two genders

4.3.2 Age and CD4 counts

The 35 patients included in the analysis were categorised into the following age groups:

- 1: 21-25yrs (n=0)
- 2: 26-30yrs (n=2; 5.7%),
- 3: 31-35yrs (n=5; 14.3%)
- 4: 36-40yrs (n=7; 20.0%)
- 5: 41-45yrs (n=5; 14.3%)
- 6: 46-50yrs (n=7; 20.0%)
- 7: 51-55yrs (n=4; 11.4%)
- 8: 56-60yrs (n=3; 8.6%) and
- 9: >61yrs (n=2; 5.7%).

The basal CD4 quadrant was not significantly affected by age (p=0.296) (see table 4.3).

Table 4.3: Baseline CD4 quadrant and age groups (N=35)

Baseline CD4 quadrant	n	Mean age group	SD	df	p
1 (1<50)	4	5.50	1.291		
2 (50<100)	3	4.33	2.517		
3 (100<200)	9	6.00	2.000		
4 (200<300)	5	5.00	2.739		
5 (>300)	14	5.00	1.664		
Total	35	5.26	1.915	34	.296

In table 4.3 the usual age groups used throughout this chapter apply (group 1: 21-25 years; group 2: 26-30 years; 3: 31-35 years; 4: 36-40 years; 5: 41-45 years; 6: 46-50 years; 7: 51-55 years; 8: 56-60 years; 9: 61 years and older). The means of the respondents' age groups in each baseline CD4 quadrant were calculated. The means of the respondents' age groups ranged from 4.33 up to 6. As the age groups in all the baseline CD4 quadrants tended towards a mean of 5, no significant differences in the means of the respondents' age groups were detected according to the baseline CD4 quadrants. Consequently, patients from similar age groups fell into all baseline CD4 quadrants, implying that no significant correlation existed between age and baseline CD4 count.

Table 4.4: CD4 change percent and age group

Age group	n	Mean CD4 change %	SD	df	p
2 (26-30yrs)	2	55.50	103.945		
3 (31-35yrs)	5	30.40	18.902		
4 (36-40yrs)	7	59.43	88.045		
5 (36-40yrs)	5	30.40	54.944		
6 (46-50yrs)	7	99.86	85.591		
7 (51-55yrs)	4	141.25	234.658		
8 (56-60yrs)	3	5.33	2.082		
9 (>61yrs)	2	29.50	13.435		
Total	35	62.00	99.584	34	.606

There was no significant difference in the CD4 change percent, as shown in table 4.4, by age group (p=0.606). In this study the baseline CD4 and CD4 increase, while on PI-based regimens, were not affected by age,

Several studies done on the effects of age on CD4 recovery while on HAART have revealed conflicting results. It was concluded in a study on ARV--naïve persons, randomly assigned to start NNRTI-based regimens, that younger age was related to

higher CD4 cell increase (Gandhi et al 2006:426-34). The Eurosida study on both NNRTI-based and PI-based regimens revealed a higher CD4 response and required a shorter time to achieve maximal CD4 levels in the respondents falling within the younger age quartiles than those falling into older age groups (Viard, Mocroft, Chiesi, Kirk, Roge, Panos, Vetter, Bruun, Johnson & Lundgren 2001:1290-1294). However, a study on long term virologically suppressed adults in Australia suggests that increasing age does not result in decreasing mean changes in CD4 cell counts (Wright, Petoumenos, Boyd, Carr, Downing, O'Connor, Grotowski & Law 2013:208-16). The John Hopkins University AIDS service, also found (Greenbaum, Wilson & Gebo 2008:2) no difference in immune response between age groups, which is similar to the finding of the current research. Smith et al (2004:1860-1868) also revealed in their study that CD4 cell increases among patients on HAART were not affected by age.

4.3.3 CD4 count change by HAART regimen

In figure 4.1, CD4 change percentage of patients on four different HAART regimens (1, 2, 3 and 10) are displayed. There was a difference between regimens by CD4 change percent (p=0.000) (see figure 4.1 and table 4.5), in decreasing order from regimens 10 (90%, SD 14.1), 2 (57.7%, SD 75.7), 3 (32.0%, SD41.7), and 1 (-9%, SD 4.4). (Regimens 4, 6, 7 and 12 were excluded from the analysis by the SPSS version 20 software due to insufficient data).

The significance in CD4 change percent between the PI-based regimens, analysed during the current study, might have been due to under representation of some regimens which were included in the analysis. The number of respondents per regimen was too small to calculate any statistical significance

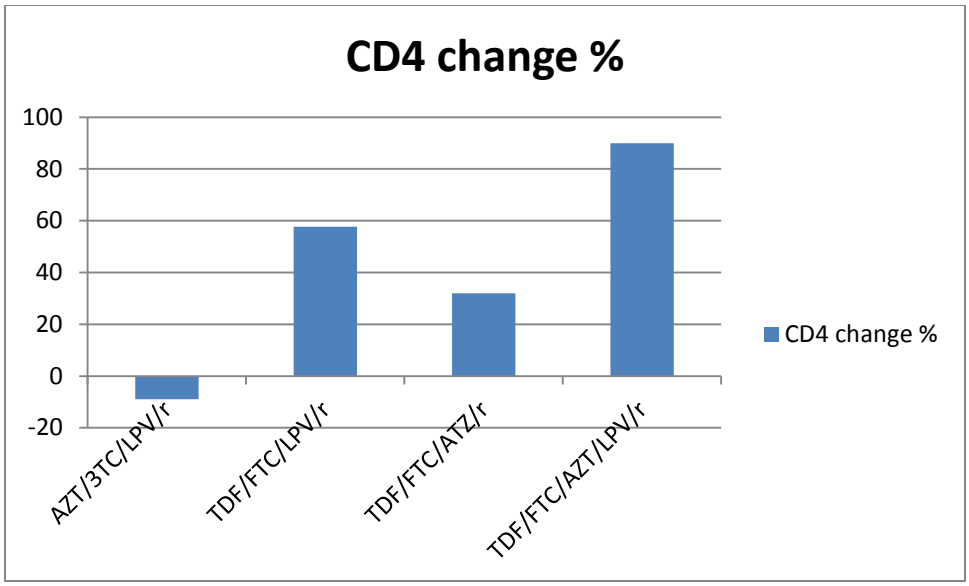

Fig 4.1 Regimen versus CD4 change percent (p=0.000) (n=27)

Table 4.5: CD4 change percent by regimen for regimens: 1, 2, 3, 4, 6, 7, 10, 12 (N=35)

REGIMEN	n	Mean CD4 Change %	SD	df	P
1 (AZT/3TC/ LPV/r)	2	-9.00	4.243		
2 (TDF/FTC/LPV/r)	23	57.70	75.789		
3 (TDF/FTC/ATZ/r)	4	32.00	41.785		
4 (TDF/FTC/DRV/r)	1	491.00	.		
6 (AZT/3TC/SQV/r)	1	13.00	.		
7 (ABC/3TC/LPV/r)	1	39.00	.		
10 (TDF/FTC/AZTLPV/r)	2	90.00	14.142		
12 (ABC/3TC/ATZ/r)	1	10.00	.		
Total	35	62.00	99.584	34	.000

Although 15 PI-based regimens were used at the center participating in this study, only patients on 8 different regimens were qualified to be included in the study, namely regimens 1,2,3,4,6,7,10 and 12 (as shown in table 4.5).

Nevertheless, regimen 10, including TDF/FTC/AZT/LPV/r, seemed to be the best regimen when compared to the others, especially with regimen 2, which included TDF/FTC/LPV/r. The strategy of adding AZT in regimen 2 to create regimen 10, known as the super second line regimen, was created based on the belief that the M184V mutation, that developed in response to treatment with FTC and 3TC, causes a viral replicative defect and improved sensitisation of the virus to AZT, d4T and TDF (Gallant 2007:453-455). However, a study in India showed no significant difference between these two regimens (Guha et al 2011). No difference in virological or immunological benefit was reportedly achieved by continuing 3TC in patients on HAART who harboured M184V mutations (Fox, Dragsted, Gerstoft, Phillips, Kjaer, Mathiesen, Youle, Katlama, Hill, Bruun, Clumeck, Dellamonica & Lundgren 2006).

There were two patients on regimen 10 included in the analysis of the current study. One patient was a male on a NNRTI-based regimen, interchanging between EFV and NVP for five years. Subsequently he had started on the supersecond line regimen 10. The reason for this choice of second line regimen was not clearly documented. The second patient on regimen 10, started on this regimen having previously failed an NNRTI-based regimen and was on a PI-based regimen in which there was only one NRTI change, and the doctor decided to place the patient on this super second line regimen 10. The superiority of regimen 10 (CD4 change of 90.0%, SD 14.1), 2 (CD4 change of 57.7%, SD75.7), is a significant finding (p=0.000) which should be further investigated if similar outcomes are observed among large numbers of patients.

Regimen 2 (CD4 change of 57.7%, SD75.7) was also superior to regimen 3 (CD4 change of 32.0%, SD41.7), and 1 (CD4 change of -9%, SD 4.4) in decreasing order of superiority. Regimen 3 has a once daily regimen compared to regimens 1, 2 and 10 that require more frequent dosages. Patients were usually placed on regimen 3 if there were fears of non-adherence due to pill burden. There were four patients on regimen 3 included in this study. All of them had prior histories of not taking their first line regimens properly. One patient had a recorded resistance testing result showing resistance to ABC, 3TC, FTC and NNRTIs. She was susceptible to TDF, AZT and PIs. She was thus

placed on TDF/AZT/ATZ/r but was not taking the regimen properly due to vomiting, a side effect of AZT, and the regimen was stopped and switched to TDF/FTC/ATZ/r. Amongst individuals with documented M184V mutations (developed in response to treatment with 3TC or FTC), with or without additional NNRTI resistance, standard three drug boosted protease inhibitor-based regimens, containing 3TC "appeared equally effective at achieving virological suppression compared with more intensive multi-drug combinations or 3TC-sparing regimens" (Highleyman 2009). In the current study it could not be ascertained if the presence of M184V in the patient concerned affected the PI-based regimen efficacy, as there was no resistance test result available for patients on the PI-based regimens. Fewer daily doses of ARVs are recommended for patients with adherence problems and patients are usually placed on this once daily regimen when they have adherence problems. The finding of lower efficacy in the once daily regimen might imply a lower adherence level to the once daily regimen by patients already known to have adherence problems.

Of the two WHO (2010:55) recommended second line regimens 1 and 2, regimen 2 (CD4 change of 57.7%, SD75.7) was apparently superior to regimen 1 (CD4 change of -9%, SD 4.4) according to the findings of this study (p=0.000). Regimen 1 has fewer daily doses (3 pills twice daily) than regimen 2 (2 pills twice daily and third pill once daily). It is uncertain if this was the reason for the significant difference in efficacy or if it was due to under representation of the number of patients on regimen 1.

A study in France compared once daily ATZ/r versus twice daily LPV/r, in combination with Tenofovir, the same as the regimens 3 and 2 respectively in the current research, and found no difference in efficacy of the regimens (Molina, Andrade-Villanueva, Echevarria, Chetchotisakd, Corral, David, Moyle, Mancini, Percival, Yang, Thirty & McGrath 2008:646-655) after 48 weeks of monitoring. The same group of patients (N=883) were followed till 96 weeks on the same regimens and there was still no difference in efficacy between the two regimens (Molina et al 2010:323-32). These studies were done on ART-naïve patients. Johnson, Grinsztejn, Rodriguez, Coco, De Jesus, Lazzarin, Lichtenstein, Wirtz, Rightmire, Odeshoo and McLaren (2006:711-8)

reported that in treatment experienced patients placed on ATZ/r versus twice daily LPV/r in combination with TDF and another NRTI, there was no difference in efficacy, and ATZ/r demonstrated fewer side effects than LPV/r. The finding of a significant difference in efficacy of these two regimens (p=0.000) in the current study differs from all these studies' reported findings. However, it should be emphasised that the current study focused on a small number of patients on different regimens, and this could have influenced the statistics.

In a study comparing once daily DRV/r with LPV/r in ART naïve patients bothin combination with TDF and FTC as in regimens 4 and 2 respectively revealed no inferiority of DRV/r compared to LPV/r (Ortiz, Dejesus, Khanlou, Voronin, Van Lunzen , Andrade-Villanueva, Fourie, De Meyer, De Pauw, Lefebvre, Vangeneugden & Spinosa-Guzman 2008). The study also revealed a more favourable safety profile of regimen 4. The same study was carried out by Mills, Nelson, Jayaweera, Ruxrungtham, Cassetti, Girard, Workman, Dierynck, Sekar, Abeele and Lavreys (2009:1979-88) and revealed once-daily DRV/r was superior in virologic response to LPV/r, with a more favourable gastrointestinal and lipid profile, confirming DRV/r as an effective, well tolerated, and durable option for ARV-naive patients. In the current study, regimen 4 was not included in the analysis by the SPSS software due to insufficient sample size, so its efficacy could not be compared to that of regimen 2.

Ferradini et al (2011:14) demonstrated a high rate of virological supression and immune reconstition after 24 months on LPV/r-based second line regimens in Cambodia. However, no comparisons were made between the four regimens included in that study: ddI/3TC/LPV$_{/r}$ (65.7%), ddI/TDF/LPV$_{/r}$ (10.0%), ddI/AZT/LPV$_{/r}$ (8.6%) and TDF/3TC/LPV$_{/r}$ (7.1%). In the current study, at six months, the mean CD4 increase was 65 cells/mm3, SD 100 and this was deemed to be an acceptable level. This means the efficacy of the PI-based regimens in use at the SFGH were at an acceptable level based on CD4 increase percent as at the end of 2013. However, regimen 10 was superior to the other 7 regimens used to treat the patients at the participating clinic, as analysed during the current study (see table 4.5).

4.3.4 Prior HAART history

The 35 patients on PI-based regimens were categorised into three groups:

- 1: patients who previously used NNRTI-based regimens only (40.0%; n=14)
- 2: patients who had previously used both NNRTI-based and PI-based regimens (40.0%; n=14)
- 3: patients who had used only PI-based regimens before starting on the current PI-based regimens (20.0%; n=7).

Table 4.6: CD4 change percent correlated with previously used ARVs (N=35)

Previously used ARVs	n	Mean CD4 change %	SD	df	p
1 (NNRTI-based only)	14	96.64	132.563		
2 (NNRTI- and PI-based)	14	23.07	23.718		
3 (PI-based only)	7	70.57	102.372		
Total	35	62.00	99.584	34	.143

When ARV experienced patients are started on second line drugs, they might have developed HIV mutation and resistance to the first line ARVs. This could affect the efficacy of their current PI-based regimens. It was based on these assumptions that the patients were categorised into three groups. However, there was no statistically significant difference in CD4 change percent in these three groups of patients; 1 (CD4 change of 96.6%, SD 132), 2 (CD4 change of 23.0%, SD23.7) and 3 (CD4 change of 70.57%, SD 102.3), (p= 0.143) (see table 4.6). Having used NNRTI-based or PI-based regimens prior to being placed on the current PI-based regimens did not have an effect on the CD4 change percent in the group of patients included in this study (N=35).

The most common mutation to NNRTIs is the K103N which occurs in 30%-50% of patients while on failing regimens with NVP and EFV (Mackie 2006). Delobel, Saliou,

Nicot, Dubois, Trancart, Tangre, Aboulker, Taburet, Molina, Massip, Marchou and Izopet (2011) investigated the impact of K103N mutation on subsequent virological response to combination ART. These authors found that one patient who had confirmed N103R mutation had a virological response to treatment with a combination of IDV (a PI), EFV and 3TC despite a high level frequency of the K103N, and this response was attributed to the PI-bsed regimen. However, that study was inconclusive. In the current study, only one patient had a resistance test confirming the presence of the N103R mutation which confers resistance to NNRTIs. Even though she was placed on once daily PI-based regimen 3, the efficacy of this regimen was less than that of regimens 10 and 2 which had higher pill loads. It is uncertain if the confirmed K103N mutation had an impact on the regimen's efficacy, or if the patient was non adherent to the PI-based regimen, having had prior episodes of non-adherence to NNRTI-based and also to the same PI-based regimens.

Buchacz, Baker, Ward, Palella, Chmiel, Young, Yangco, Novak and Brooks (2012:230290) reported a decrease in the PI resistance in PI experienced patients from 71% to 46% since the increased use of RTV-boosted PIs from 5% to 81% during the period 1999-2008. Several studies have been collated on the response to new PI-containing regimens in patients with PI-resistance mutations (PI-resistance mutations. Phenotypic susceptibility scores predict HIV response in PI-experienced patients (Swanstrom, Bosch, katzenstein, Cheng, Liang, Hellmann, Haubrich, Fiscus, Fletcher, Acosta & Gulick 2004:886-893). Documented mutations at protease positions 10, 20, 24, 33, 36, 47, 48, 54, 82 and 84 were associated with virological resistance to LPV/r (Grant, Wong, Rode, Shafer, De Luca, Nadler, Hawkins, Cohen, Harrington, Kempf & Zolopa 2008:4050-6; King, Rode, Cohen-Codar, Calvez, Marcelin, Hanna & Kempf 2007:3067-74). In the current study, baseline resistance results were not taken into consideration because it was not done for all the patients included in the study. If prior use of NNRTI or PI had significantly affected the CD4 change percent, they might have developed resistance to the previously used regimens

The effect of prior regimens used by the patients included in this study, on their immunologic recovery might be related to the history of changing all NRTIs or not to do so, regimens previously confirmed failed, prior non-adherence to PIs and previously switching between PI regimens, which will be discussed in later sections of this report.

4.3.5 CD4 change percent and changing all NRTIs

It is recommended by the WHO (2010:53-57) that the NRTI backbone used in first line regimens, should be changed when starting a new second line regimen, as mutations might have developed in response to the first line NRTIs. In order to test whether or not this affected the efficacy of the regimens, the 35 patients on the current PI-based regimens were categorised into two groups:

- 1: all NRTIs changed (f=26; 74.3%)
- 2: all NRTIs not changed (f=9; 25.7%)

Table 4.7: CD4 change percent and changing of all NRTIs (N=35)

All NRTIs changed	n	Mean CD4 change %	SD	df	p
1 (yes)	26	55.08	96.753		
2 (no)	9	82.00	110.849		
Total	35	62.00	99.584	34	.493

There was no statistically significant difference in CD4 change percent between the two groups; 1 (CD4 change of 55.0%, SD 96.8) and 2 (CD4 change of 82.0%, SD 110.8), (p=0.493) (see table 4.7). In this study, after using first line medications, changing all the NRTI backbone or not doing so had no effect the CD4 change percent when the 35 patients commenced PI-based second line regimens.

The finding of no significance was in keeping with other research findings. Medecins Sans Frontieres documented favourable outcomes observed in PI-based second-line regimens with at least one NRTI change. Hull et al also demonstrated that amongst individuals with documented M184V mutations (developed in response to treatment with 3TC or FTC), with or without additional NNRTI resistance, standard three drug boosted protease inhibitor–based regimens containing 3TC, “appeared equally effective’’ at achieving virological suppression compared with more intensive multi-drug combinations or 3TC-sparing regimens. These statements are similar to the findings in the current research. This means starting second line PI-based regimens is feasible in resource-limited settings with a limited number of available NRTIs, with outcomes which may be similar to that in resource-rich countries where several alternative NRTIs are available (Highleyman 2009; Pujades-Rodríguez et al 2008:1305-1312).

4.3.6 Prior non adherence to PIs

Confirmed failure to any regimen involves confirmed adherence to that regimen, with virological, immunological and sometimes clinical failure on treatment with that specific regimen. Resistance studies could also confirm the presence of resistance mutations. Non adherence might lead to the development of drug resistance.

Table 4.8: CD4 change percent and prior non adherence to PIs (N=35)

Prior non-adherence to PI	n	Mean CD4 change %	SD	df	p
1 (yes)	10	46.20	87.049		
2 (no)	25	68.32	105.175		
Total	35	62.00	99.584	34	.561

Patients were started on their current PI-based regimens for reasons including failure on first line NNRTI-based regimens (68.5%; n=24), toxicity of NNRTI (14.2%; n=5), or prior PI-based regimens (n=3; 8.6%), to reduce pill burden of prior PI-based regimens (2.9%; n=3), pregnancy (5.7%; n=2), tuberculosis treatment (5.7%; n=2), transferred from other

health care facilities already on PIs (5.7%; n=2) and in one patient's file, the reason stated was "uncertainty". Some of these patients were started on their current PI-based regimens for more than one of the recorded reasons. No patient had documented confirmation of failure to PI-based regimens before starting his/her current PI-based regimens. However, in some patients who were non-adherent to previous PI-based regimens, it was assumed that there was the possibility of some resistance mutations to PI-based medications. It was based on this that the 35 patients on current PI-based regimens were categorised into two groups:

- 1: prior non adherence to a PI-based regimen (28.6%. n=10)
- 2: no prior non adherence to a PI-based regimen (71.4%; n=25)

There was no statistically significant difference in CD4 change percent between the two groups; 1 (CD4 change of 46.2%, SD 87.0) and 2 (CD4 change of 68.3%, SD 105.1) (p= 0.561) (see table 4.8). Thus having a history of non-adherence to previous PI-based regimens did not affect the CD4 change percent in the current PI-based regimens. PIs are known to have high genetic barriers to developing resistant mutations, and this may be the reason for the non-significance of prior PI non-adherence. However, resistance tests were not done for all the patients before starting on the current PI-based regimens so an assessment of the effect of any mutations which confer resistance to PIs was impossible (Demeter et al 2008; WHO 2010: 55-56).

4.3.7: CD4 change percent correlated with being on a failing regimen just before switching to the current PI-based regimen

All the patients were HAART experienced. Some were on successful HAART medications, but were switched to their current PI-based regimens for reasons including failure on first line NNRTI-based regimens (n=24;7%), toxicity of NNRTI (5;1%), or prior PI-based regimens (3; 9%), to reduce pill burden of prior PI-based regimens(1; 3%), pregnancy (2; 6%), tuberculosis treatment (2; 6%), transferred in already on PIs (2; 6%) and in 1(3%) patient, the reason started on the current PI-based regimen was uncertain.

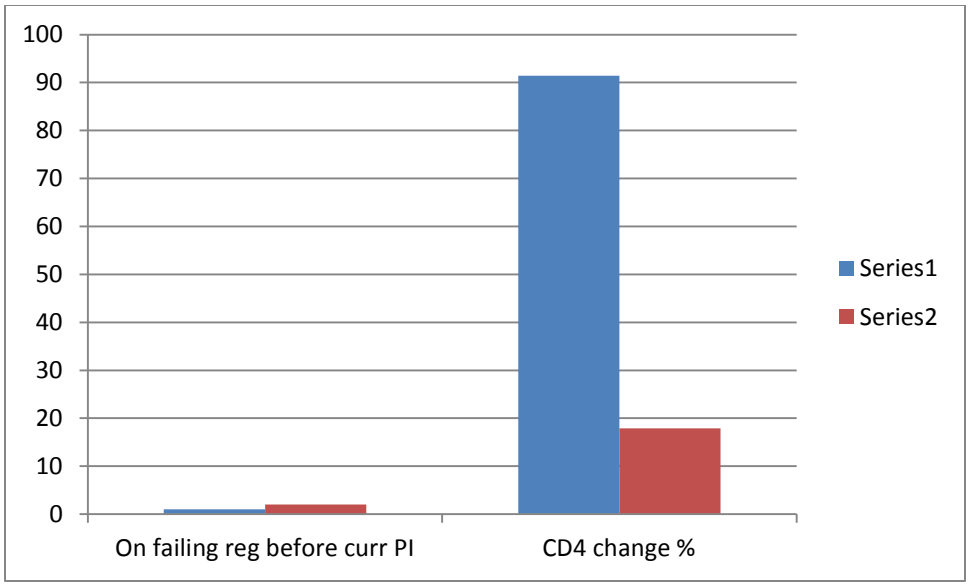

Figure 4.2: CD4 change percent and being on a failing regimen before current PI (N=35)

Some patients started their current PI-based regimens for more than one of the recorded reasons. The 35 patients on current PI-based regimens were categorised into two groups based on whether or not they were on failing regimens just before their current PI regimens:

● 1: they were on failing regimens just before their current PI-based regimens (60.0%; n=21)

● 2: they were not on failing regimens just before their current PI-based regimens (40.0%; n=14)

Table 4.9: CD4 change percent and use of a failing regimen just before current PI regimen (N=35)

On failing regimen just before current PI	n	Mean CD4 change %	SD	Df	p
1 (yes)	21	91.4	119.129		
2 (no)	14	17.9	24.610		
Total	35	62.0	99.584	34	.030

This categorisation was based on records written by the doctors on the patients' files. There were 21 (60.0%) patients in group 1 and 14 (40.0%) patients in group 2. There was a statistically significant difference in CD4 change percent in the two groups; 1 (CD4 change of 91.4%, SD 119.1) and 2 (CD4 change of 17.9%, SD 24.6) (p= 0.03) (see figure 4.2 and table 4.9), indicating that patients who were on failing regimens before their current PI-based regimens had a higher CD4 change percent than those who were on successful regimens. Of note is that patients on failing regimens were expected to have lower baseline CD4 counts before commencing their current PI-based regimens. The next section (4.3.8) attempts to make a connection between the two variables: on failing regimen before current PI-based regimens and baseline CD4. The baseline CD4 has also been related to CD4 change percent in several studies and this will be addressed in section 4.3.8.

4.3.8 Baseline CD4 and failing regimen just before current PI

When the CD4 baseline quadrants were compared on the variable whether the patients were on failing regimens just before starting current PI-based regimens, there was a statistically significant difference between the two groups (p=0.021) (see figure 4.4 and table 4.10). The patients who were on successful regimens (group 2), had the higher baseline CD4 quadrant. This difference was expected, as patients on failing regimens were expected to have lower CD4 values.

The correlation between having a lower CD4 baseline quadrant and being on a failing regimen just before current PI-based regimens was also expected to be reflected in the CD4 change percent compared to baseline CD4 quadrants. This is the case as patients on a failing regimen before their current PI-based regimens, have been shown to have significantly higher CD4 change percent than patients not on failing regimens (p=0.030) as discussed in section 4.3.7. This is addressed in the next section.

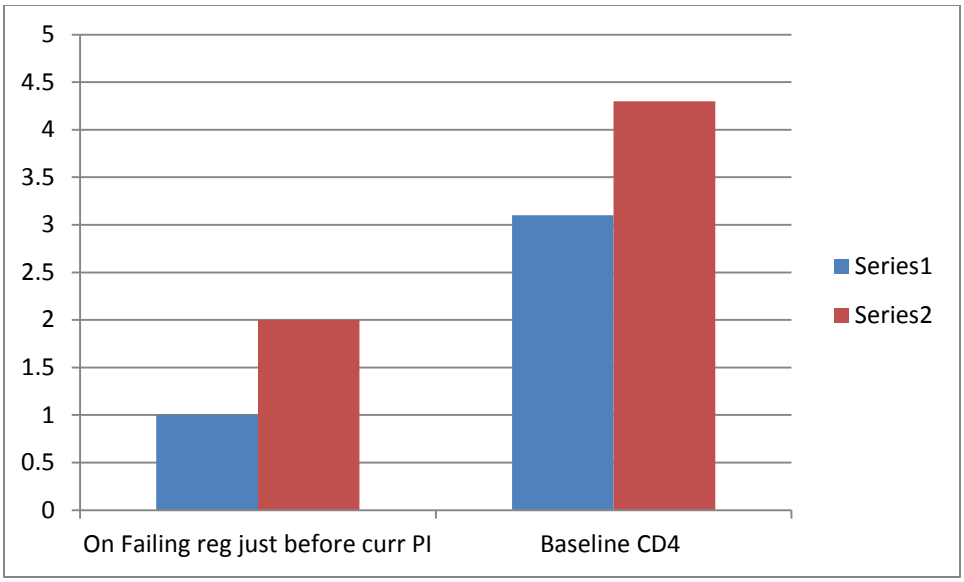

Fig 4.3 Baseline CD4 quadrant and being on failing regimen just before current PI-based regimen p=0.021. On failing regimen just before current PI: 1(yes) and 2(no). Baseline CD4 Quadrants: 1<50, 2=50-100, 3=100-200, 4=200-300 and 5>300 cells/mm^3

Table 4.10: Baseline CD4 and failing regimen just before commencing with the current PI (P=0.02). On failing regimen just before current PI: 1(yes) and 2(no). Baseline CD4 Quadrants: 1<50, 2=50-100, 3=100-200, 4=200-300 and 5>300 cells/mm^3

On failing regimen just before current PI	n	Mean	SD	Df	p
1 (yes)	21	3.10	1.480		
2 (no)	14	4.43	.756		
Total	35	3.63	1.395	34	.021

4.3.9 Baseline CD4 quadrant and CD4 change percent

The 35 patients on current PI-based regimens were grouped according to their baseline CD4 by categorising them into five groups, as shown in table 4.1. There was a statistically significant difference in CD4 change percent in these groups; 1 (CD4 change of 237.5%, SD 180.3), 2 (CD4 change of 97.0%, SD 33.6), 3 (CD4 change of 62.44%, SD 87.3), 4 (CD4 change of 18.8%, SD 44.8) and 5 (CD4 change of 19.5%, SD 22.7) (p=0.000) (see fig 4.4 and table 4.11). The CD4 change percent was highest in the lowest baseline CD4 quadrant, and was in decreasing order from 1, 2, 3, 4 and 5. This means patients starting their PI-based regimens at lower CD4 levels achieved a higher CD4 change percent than patients with higher baseline CD4. After examining the results of section 4.3.7 (CD4 change percent was higher in patients failing regimen just before switching to current PI-based regimen (p=0.03)) and 4.3.8 (baseline CD4 was lower in patients failing regimen just before current PI (p=0.021)), this correlation was expected in this section.

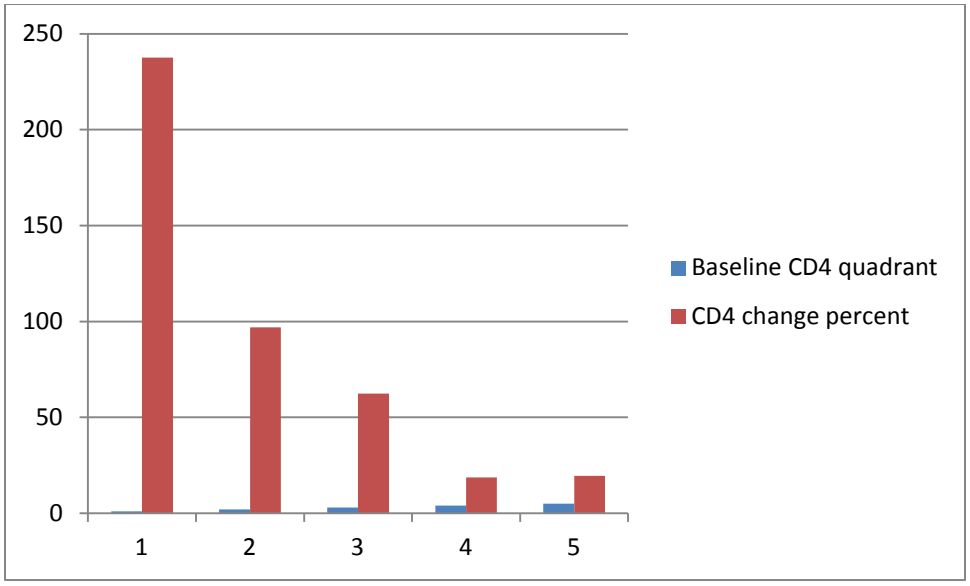

Fig 4.4 CD4 change percent and baseline CD4 quadrants (p= 0.000) (N=35)

Table 4.11: Baseline CD4 quadrant and CD4 change percent (N=35)

Baseline CD4 quadrant	n	Mean	SD	Df	p
1	4	237.50	180.352		
2	3	97.00	33.601		
3	9	62.44	87.396		
4	5	18.80	44.824		
5	14	19.50	22.698		
Total	35	62.00	99.584	34	.000

Literature reveals conflicting reports about the effect of baseline CD4 on immune recovery. Smith et al (2004:1860-1868) revealed that CD4 cell increases on HAART were higher in patients with lower baseline CD4 counts. Lawn, Myer, Bekker and Wood (2006:6-59) also reported a higher CD4 cell recovery on ART in patients with lower CD4 counts at baseline. These were similar to the findings of this study where the patients at lower baseline CD4 counts achieved significantly (p=0.000) higher CD4 change percent than those who started at higher baseline CD4 cell counts. However, a study comparing CD4 increase on NNRTI-based regimens revealed higher CD4 cell increase in patients with higher baseline CD4 counts (Gandhi et al 2006:426).

It is possible that the results of the current study were arrived at because some patients were on successful regimens before starting their current PI-based regimens, and had normal CD4 levels. Due to the normal variation in CD4 counts, the CD4 level might have swayed up or down in patients whose CD4 levels had been normalised. There were no CD8 values recorded for these patients to confirm who had a normal variation or an actual decreased CD4 count.

4.3.10 CD4 change percent and period without ARVs

Table 4.12: CD4 change percent and no-ARVs period before current PI regimen (N=35)

No ART period before starting PI	n	Mean	SD	df	p
1 (yes)	5	78.40	119.812		
2 (no)	30	59.27	97.942		
Total	35	62.00	99.584	34	.697

Table 4.13: Baseline CD4 quadrant and period off ART before current PI-based regimens (ANOVIA). Baseline CD4 Quadrants: 1<50, 2=50-100, 3=100-200, 4=200-300 and 5>300 cells/mm^3

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.005	1	.005	.002	.961
Within Groups	66.167	33	2.005		
Total	66.171	34			

Some patients who had to be started on their current PI-based regimens were off ARVs for a period before commencement of their current regimens. The 35 patients on current PI-based regimens were categorised into two groups based on whether there was a period of no ART before starting current PI-based regimens. Five (14.3%) patients discontinued taking ARVs while 30 (85.7%) patients had no such ART discontinuation. Two patients defaulted on their PI-based regimens for no obvious reason; one patient had stopped taking her ARVs because she used it for PMTCT which was stopped after delivery (period off ART=22 months) and another patient was on PI-based regimen for resistance to NNRTI but defaulted on his own (period off ART=36 months). One patient

was placed on a PI-based regimen because he had TB, but he was non-compliant and the doctor stopped him (period off ART=5 months). The other two patients stopped because they experienced side effects caused by LPV/r and were later restarted on the same regimens (period off ART=24 and 2 weeks respectively).

It is assumed that a period on no ART might contribute to a drop in baseline CD4 and thus to the CD4 change percent when restarted on HAART. There was no statistically significant difference in CD4 change percent in these two groups (p=0.697) (see table 4.12). Having a no-ART period before restarting the current PI-based regimens did not affect the CD4 change percent of the patients on these PI-based regimens.

The two groups were then compared based on their baseline CD4 quadrants. There was no statistically significant difference in the CD4 baseline quadrants of the two groups (p= 0.961) (see table 4.13). It would have been expected that patients who were off ARVs for a period of time would have a lower basal CD4 quadrant, but this was not the finding in this research. These patients were probably not on successful regimens before their previous ARVs were stopped, so they might have been comparable in their basal CD4 quadrant to patients on ineffective HAART who might also have been classified as being on failing regimens just before their current PI-based regimens were commenced. Or maybe these patient did not have an absolute need for ART for immune reconstitution at the time they were started on it. Of the five patients who were off ART, only one (patient 22) had confirmed failure and resistance to first line NNRTI regimen necessitating him to start on a PI-based regimen.

4.3.11 CD4 change percent and previously failed regimens

Confirmed failure on any regimen involves confirming virological and immunological failure on a regimen to which the patient is adherent. This information was obtained from the doctor’s documentation on the medical records of the patients

Table 4.14: CD4 change percent and prior regimens failed (N=35)

Prior regimens failed	n	Mean CD4 change %	SD	df	P
0 (never any prior failure)	9	22.11	27.200		
1 (prior failure)	26	75.81	111.710		
Total	35	62.00	99.584	34	.167

The 35 patients on current PI-based regimens were categorised into three groups, based on their failed regimens before their current PI-based regimens.

- 0: never failed any regimens (25.7%; n=9)
- 1: previously failed NNRTI-based regimens (74.3%; n=26)
- 2:previously failed both NNRTI and PI based regimens (n=0)

None of the patients had previously failed a PI regimen. Only two groups, 0 and 1 were compared. There was no statistically significant difference in CD4 change percent in the two groups; 1 (CD4 change of 22.1%, SD 27.2) and 2 (CD4 change of 75.8%, SD111.7) (P= 0.167). Baseline resistance testing was not done in this research. Patients who had failed the NNRTI-based regimens might have developed resistant mutations to NNRTIs. Since this did not affect the CD4 change percent on the current PI-based regimen, it could be assumed that resistant mutations to NNRTI did not affect the PI-based regimen efficacy. This is similar to the finding in the study by Delobel et al (2011) who investigated the impact of K103N mutation on subsequent virological response to combination ART. These authors found that one patient who had confirmed N103R mutation, had a virological response to treatment with a combination of IDV (a PI), EFV and 3TC despite a high level frequency of the K103N, and this response was attributed to the PI-based regimen.

Several studies have examined the effect of previously used regimens on PI efficacy. Documented mutations at protease positions 10, 20, 24, 33, 36, 47, 48, 54, 82 and 84 were associated with virological resistance to LPV/r (Grant et al 2008:4050-6; King et al 2007:3067-74). In the current research, baseline resistance results were not taken into consideration because it was not done for all the patients included in the study. No patient had a history of having failed on a PI-based regimen. Thus there was no reason to suspect that the 35 patinets participating in the current study harboured PI resistant mutations.

4.3.12 Previous switches between PI regimens

Patients who had used other PI-based regimens before the current one (22.9%; n=8) were switched for prior PI non availability (25%; n=2), prior PI non-adherence (25%; n=2), commenced TB treatment (12.5%; n=1), side effects of prior PI-based regimens (37.5%; n=3) and at the patient's request (25%; n=2). Some patients switched regimens for more than one reason. The 35 patients on current PI-based regimens were grouped into two groups based on whether they previously switched between PI-based regimens or not.

Table 4.15: CD4 change percent and history of switching PIs. Switched PIs (N=35)

Switched btw PIs	N	Mean CD4 change %	SD	Df	P
1 (yes)	8	12.13	15.376		
2 (no)	27	76.78	109.144		
Total	35	62.00	99.584	34	.108

There was no statistically significant difference in CD4 change percent in the two groups; 1 (CD4 change of 12.1%, SD 15.4) and 2 (CD4 change of 76.8%, SD109.1) (p= 0.108). Prior use of PI-based regimens before commencing with the current PI-based regimens did not affect the CD4 change percent on the current PI-based regimens. This

relation was important because if the patient failed on a previous PI-based regimen, the patient might have developed resistant mutations to the previous PI-based regimen and the effect of that on the current PI-based regimen might have been noticed in the CD4 change percent. None of the eight (22.9%) patients who switched PIs had done so for failure of a previous PI-based regimen. Even though two patients were switched PI-based regimens for non-adherence to their regimens, this did not affect the efficacy of the subsequent PI-based regimen, possibly due to the PI's high genetic barrier to resistance (Demeter et al 2008). Resistance tests were not routinely done before starting any new regimen so it could not be determined if any resistant mutations developed due to use of previous PI-based regimens.

4.3.13 Regimens and baseline CD4 quadrant

As it appeared the baseline CD4 count was significant in the CD4 change percent (p=0.000), an analysis was carried out to determine if there was a difference in baseline CD4 counts between regimens. There was no significant difference between the baseline CD4 count of the regimens (p=0.323) (see table 4.16), thus this possible confounder did not account for the difference in efficacy between the regimens.

Table 4.16: Correlation of Baseline CD4 quadrant and regimen (N=35)

REGIMEN	n	Mean	SD	df	P
1 (AZT/3TC/ LPV/r)	2	5.00	.000		
2 (TDF/FTC/LPV/r)	23	3.70	1.490		
3 (TDF/FTC/ATZ/r)	4	3.50	.577		
4 (TDF/FTC/DRV/r)	1	1.00	.		
6 (AZT/3TC/SQV/r)	1	5.00	.		
7 (ABC/3TC/LPV/r)	1	3.00	.		
10 (TDF/FTC/AZTLPV/r)	2	2.50	.707		
12 (ABC/3TC/ATZ/r)	1	4.00	.		
Total	35	3.63	1.395	34	.323

4.3.14 Viral load

VL was recorded as undetected once it was less than 400/ml for the 35 patients included in this study. Undetectable viral load is required for immune recovery. All the patients who had VL results at six months had undetectable VL so this parameter was not used for comparing the outcomes of the different regimens. However, it could be concluded that all 35 patients achieved an acceptable level of efficacy on their PI-based HAART regimens after six months on treatment by having undetectable VL counts.

Table 4.17: Viral blip and regimen

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	.417	7	.060	.691	.679
Within Groups	2.326	27	.086		
Total	2.743	34			

Viral blips are isolated elevations in VL that do not predict subsequent virological failure (CDC 2013). Low levels (50-1000 copies/ml) have been found frequently and are short lasting, with no effect on clinical stage while high level viraemia (>1000 copies/ml) was more frequently associated with resistance and therapy changes (Van Sighem, Zhang, Reiss, Gras, Van der Ende, Kroon, Prins & De Wolf 2008:104-8).

Of the 35 patients included in the study, two patients had virological blips recorded in their files during treatment on their PI-based regimen one at 18 months (a female, VL=1503 copies/ml) and the other at 12 months (a male, VL=708copies/ml).The female was on regimen 1 and the male was on regimen 2. Both had recorded undetectable VL at six months on their PI-based regimens and the VL repeated after three months of the blip were undetectable for both patients. The female patient had a higher viral blip and

admitted to having had unprotected sex at the time when the viral blip was detected. There was no statistically significant incidence of viral blip by regimen (p=0.679). So none of the regimens were more likely than others to lead to regimen failure.

4.3.15 The correlation of anaemia with PI-based regimens

Haemoglobin levels of less than 10 mg/dl were taken as indicating anaemia. A total of 30 patients included in this research had baseline and follow up haemoglobin levels recorded at 6, 12 and 18 months. Only one patient out of these 30 had developed anaemia after starting the PI-based regimen.

Table 4.18: The development of anaemia on different regimens (n=30)

	Frequency	Percent	Valid Percent	Cumulative Percent
1(yes before starting regimen)	1	3.3	3.3	3.3
2 (yes after starting regimen)	1	3.3	3.3	6.7
3 (did not develop anaemia)	28	93.3	93.3	100.0
Total	30	100.0	100.0	

These 30 patients (with haemoglobin records) were categorised into three groups based on whether they had anaemia or not:

- 1: yes, before starting the PI-based regimen (3.3%; n=1)
- 2: yes, after starting the PI-based regimen or (3.3%; n=1)
- 3: did not develop anaemia (93.3%; n=28)

4.3.16 Renal impairment on PI-based regimens

Persistent Creatinine levels above 2.0mg/dl were regarded as renal impairment. No patient included in this study had renal impairment before or during treatment with their current PI-based regimens.

4.3.17 High lipids on PI based regimen

Elevated lipids are a known side effect of the Protease inhibitor class. Cholesterol and triglyceride levels above 200mg/dl were regarded as being elevated.

Table 4.19: Increased cholesterol levels on PI-based regimens

Developed high cholesterol levels	Frequency	Percent	Valid Percent	Cumulative Percent
1 (yes before starting regimen)	2	6.5	6.5	6.5
2 (yes after starting regimen)	2	6.5	6.5	12.9
3 (did not develop high cholesterol)	27	87.1	87.1	100.0
Total	31	100.0	100.0	

Patients were categorised into three groups based on whether they had increased lipids while on their PI based regimens.

- 1: increased lipids before starting the regimen
- 2: increased lipids after starting regimen
- 3: did not develop increased lipids.

Table 4.20 Increased triglyceride levels on PI-based regimens

	Frequency	Percent	Valid Percent	Cumulative Percent
1 (yes before starting PI-regimen)	2	6.7	6.7	6.7
2 (yes after starting PI regimen)	5	16.7	16.7	23.3
3 (no did not develop high triglycerides)	23	76.7	76.7	100.0
Total	30	100.0	100.0	

4.4 OVERVIEW OF RESEARCH FINDINGS

The total efficacy of all the PI-based regimens in use at the SFGH was at an acceptable level. It met the required standards of undetected VL by six months for all the patients, and the average CD4 cell increase was 65, SD 99.8 after six months on HAART. There was a significant difference in potency of the regimens (p=0.000).

Regimen 10 was the most potent (p=0.000), but it is uncertain if this was a due to non-representation of the other regimens due to small numbers of patients in the different regimen groups. The most important variable which seemed to affect CD4 change percent was the baseline CD4 (p=0.000) which was also significantly related to whether or the patient was on a failing regimen before starting the current PI-based regimen (p= 0.021). There was no statistically significant difference in the baseline CD4 counts of patients on the different regimens (p=0.323). Hence it was inferred that, even though lower baseline CD4 was associated with higher CD4 change percent (p=0.000), the difference in efficacy of the regimens (p=0.000) was not attributable to the patients' baseline CD4 counts when they started on the PI-based regimens.

In the current research, other factors such as age (p= 0.606), gender (p=0.698), prior use of ARVs (p= 0.143), change of all NRTIs or not (p=0.493), prior failed regimens (p= 0.167), and prior non adherence to PIs (p=0.561) did not have any significant effect on CD4 change percent.

4.5 SUMMARY

A repeat study needs to be carried out to examine the specific potency of the regimens and the CD4 change percent and related variables as these results will have a great impact in the improvement of patient care.

CHAPTER 5

CONCLUSIONS, RECOMMENDATIONS AND LIMITATIONS OF THE STUDY

5.1 INTRODUCTION

The purpose of the study was to compare patients' treatment outcomes (CD4 cell count and VL six months after commencing treatment) of the PI-based (second line) HAART regimens in Trinidad. It was impossible to evaluate the clinical outcomes (WHO stages) because these were not recorded on the patients' files. The impact of the following variables that could impact on these treatment outcomes were considered: patients' treatment adherence levels, baseline as well as subsequent CD4 counts and VL levels, and OIs.

5.2 CONCLUSIONS

The conclusions will be presented according to the objectives stated in section 1.4.2 of this thesis. Gender had no impact on baseline CD4 quadrant (P=0.537) and CD4 change percent (p=0.698) on the treatment outcomes of the current PI-based regimens. Age also had no effect on baseline CD4 quadrant (p=0.296) and CD4 change percent (p=0.606) in patients on PI-based regimens in the current research.

Several variables, identified in the literature review, could not be tested in the current study. Diurnal variations in CD4 levels were not applicable as all the tests were scheduled to be done during the morning hours at the HIV clinic of the SFGH on the patients' scheduled testing dates. Laboratory variations were also not applicable as all

the tests were done by the same laboratory. Weight and staging were not compared for the patients on the PI-based regimens because these were not recorded for all the patients. The known damaging effect of corticosteroid and interferon administration were not investigated as there were no records of patients using these drugs.

5.2.1 Baseline CD4 and VL counts compared with these counts at 6, 12 and 18 months of treatment on PI-based HAART regimens

Due to the quality of records in the patients' files, CD4 and VL counts could only be determined at baseline and at 6 months' PI-based HAART. Consequently the initial objective of measuring these outcomes at 12 and 18 months after commencing PI-based HAART regimens had to be abandoned.

Patients with lower baseline CD4 had a higher CD4 change percent than those with higher baseline CD4 (P=0.000). The most important factors which seemed to affect CD4 change percent were the regimen in use and the basal CD4 at which the PI-based regimens were started. The factor found to be directly related to the baseline CD4 was being on a failing regimen just before commencing the current PI-based regimen. Patients on failing regimens had lower baseline CD4 quadrants and a higher CD4 change percent on their PI-based regimens than patients falling in the higher CD4 quadrants.

Factors found to have no effect on regimen efficacy included prior HAART history, changing all NNRTIs or not, prior non adherence to PIs, a period on no ART before the current PI-based regimen, previously failed regimens and previous switches between PI-based regimens

5.2.2 HAART adherence levels as measured by regular clinic attendance

Having a history of non-adherence to previous PI-based regimens did not affect the CD4 change percent in the current PI-based regimens. PIs are known to have high genetic barriers to developing resistant mutations, and this might be the reason for the

non-significance of prior PI-based HAART regimens and non-adherence. However, resistance tests were not done for all the patients, before starting on the current PI-based regimens, so an assessment of the effect of any mutations which might cause resistance to PIs was impossible

5.2.3 The World Health Organization developmental stage of AIDS

This could not be determined as the WHO developmental stage of AIDS was not recorded in the patients' files. Consequently no relevant information could be used from these files to identify whether the patients' WHO developmental stage of AIDS improved after being put on PI-based HAART regimens.

5.2.4 Opportunistic infections

No information was reported in the patients' files about OIs. Consequently this objective, of correlating the occurrence of OIs with PI-based HAART outcomes, could not be realised.

5.2.5 Side effects of PI-based HAART regimens as reported by the patients

The patients' records were scrutinised for side effects of anaemia, renal impairment and increased lipids while on treatment with their current PI-based regimens. One patient (3.3%) had anaemia before commencing on the current PI-based regimen. One patient (3.3%) had anaemia after commencing on the current PI-based regimen. Twenty eight patients (93.3%) did not have any documentation of anaemia.

There was no patient with recorded renal impairment on any of the regimens.

Two patients (6.5%) had high cholesterol levels before commencing the current PI-based regimen. Two patients (6.5%) had high cholesterol levels after commencing the current PI-based regimen. Twenty seven patients (87.1%) did not have any

documentation of high cholesterol. Two patients (6.7%) had high triglyceride levels before commencing on the current PI-based regimen. Five patients (16.7%) had high triglyceride levels after commencing on the current PI-based regimen. Twenty three patients (76.7%) did not have any documentation of high triglyceride.

5.2.6 Deaths of patients on PI-based HAART regimens

No death was recorded in the 35 respondents' files. This might have been a shortcoming of the study design because only records of patients attending the participating HIV clinic were studied.

5.2.7 Reasons why patients were put on specific 2nd line HAART regimens

Patients were started on their current PI-based regimens for reasons including failure on first line NNRTI-based regimens (68.5%; n=24), toxicity of NNRTI (14.2%; n=5) or prior PI-based regimens (n=3; 8.6%), to reduce pill burden of prior PI-based regimens (2.9%; n=3), pregnancy (5.7%; n=2), tuberculosis treatment (5.7%; n=2), transferred from other health care facilities already on PIs (5.7%; n=2) and in one patient's file, the reason stated was "uncertainty". Some of these patients were started on their current PI-based regimens for more than one of the recorded reasons. However, the records in the patients' files did not indicate on which grounds any specific PI-based regimen was selected for a specific patient.

Two patients were started on a PI-based regimen due to pregnancy. One patient defaulted several times but later became compliant several years after the pregnancy. A connection could not be made between her pregnancy and her regimen efficacy. The other patient was switched to the current PI-based medication just for the duration of the pregnancy, on regimen 1. She was previously on a successful NNRTI-based regimen before the pregnancy. She maintained high CD4 and undetected viral load, before, during and after the pregnancy. There was no effect recorded of the pregnancy on her immunologic or virological status on the current PI-based regimen.

5.2.8 Patients' periods of failing on 1st line HAART regimens before being changed to a PI-based HAART regimen

There was no statistically significant difference in CD4 change percent based on prior regimens used (p= 0.143). All the patients were treatment experienced. Some had used NNRTI-based regimens only (n=14; 40.0%), a second group (n=14; 40.0%) had used both NNRTI and PI-based regimens, and a third group had previously used only PI-based regimens (n=7; 20.0%). This question was also related to whether the patient changed all NRTIs when starting the current regimen, history of prior non adherence to PIs, history of switching PI-based regimens and history of having confirmed failure to a previous regimen by virological, immunological and clinical findings.

Changing all the NRTIs previously used when starting the current PI-based regimen did not make any statistically significant difference in CD4 change percent (p= 0.493). This means starting second line PI-based regimens is feasible in resource-limited settings with a limited number of available NRTIs, because these outcomes were similar to those of resource-rich countries where several alternative NRTIs are available.

The 35 patients included in the study were split in two groups based on history of switching PI-based regimens; 1: yes previously switched PIs (f=8; 22.9%) and 2: no, did not previously switch PIs (f=27; 77.1%), and there was no statistical significance between the groups in CD4 change percent (P=0.108). Patients who had used other PI-based regimens before the current one (8; 22.9%) were switched for prior PI non availability (2; 25%), prior PI non adherence (2; 25%), commenced TB treatment (1; 13%), side effects of prior PI-based regimens(3; 38) and at patients request (2; 25%), some cases being for more than one reason. None of the 8 (22.9%) patients who switched PIs were switched for failure of a previous PI-based regimen. Even though 2 patients were switched for non-adherence to their regimens, this did not affect the efficacy of the subsequent PI-based regimen. This may have been due to the PI high genetic barrier to resistance. Resistance tests were not routinely done before starting

any new regimen so it could not be determined if there was any resistant mutations developed due to use of previous PI-based regimens.

There were n=9; 25.7% patients who had never failed any regimens and n=26; 74.3% patients who had previously failed on NNRTI-based regimens. No patients failed on PI-based regimens. Having confirmed failure to a previous regimen did not affect CD4 change percent in the current study (P=0.167). Having failed previous NNRTI-based regimens did not significantly affect CD4 change percent of current PI-based regimens. This was an expected finding because resistance to NNRTI has not been shown to confer resistance to PIs.

There was no statistically significant difference in the CD4 baseline quadrants (p= 0.961) and CD4 change percent (p= 0.697) when the patients were split in two groups based on whether they had been off ART (n=5, 14.3%) or not (n=30, 85.7%) for a short period before commencing the current PI-based regimens. The most likely reason was determined to be that these patients were not on successful regimens before their previous drugs were stopped, so they may have been comparable in their basal CD4 quadrant to patients on ineffective HARRT who may also have been classified as being on failing regimen just before the current PI based regimens. However patients on failing regimens in this research had lower baseline CD4 (P=0.02) and higher CD4 change percent (p=0.03).It was expected that patients who were off ART for a period before commencing on their current PI-based regimens would have a lower baseline CD4 quadrant due to the natural progression of HIV/AIDS in which there is usually declining CD4 and rising viral load but the findings of this study did not show that trend.

5.2.9 A comparison of the treatment outcomes of different PI-based regimens

The CD4 and VL recovery of all 35 patients on PI-based regiments, included in this study, were of acceptable levels after 6 months' treatment as all these patients had undetectable VL after 6 months' treatment. The PI-based regimens in use at the SFGH have an acceptable level of efficacy.

The finding of higher efficacy of regimen 10 than 2 (TDF+FTC+LPV/r) (P=0.000) is significant (see table 4.5 indicating the CD4 change percent by regimens for eight PI-based HAART regimens). Of note is that 23 patients were on regimen 2 while only 2 were on regimen 10, so this difference might be due to under representation of regimen 10. Both of the patients on regimen 10 were on failing regimens before starting their current regimens. Those patients on failing regimens had a higher CD4 change percent. This was also related to the significantly lower basal CD4 quadrant seen in patients who were on failing regimen just prior to their current PI-based regimens (P=0.021), and the finding that patients with lower basal CD4 had a significantly higher CD4 change percent than those with higher basal CD4 counts (P=0.000).

To identify whether or not baseline CD4 acted as a confounding variable influencing the efficacy of the regimens, the basal CD4 of the regimens were compared. There was no statistically significant difference (P= 0.323). Thus the baseline CD4 counts could not explain the differences in efficacy of the regimens. The theoretical assumption that patients with M184V mutations, from having failed 3TC or FTC, have reduced HIV replicative property and increased susceptibility to AZT, might explain the higher efficacy of regimen 10.

The overall efficacy of the PI-based regimens was up to an acceptable standard. Patients on successful regimens were expected to have undetected VL by six months on HAART and CD4 increase of at least 50cells/mm^3 after six months. In this study, all the patients had undetected VL by six months and the CD4 increase was M=65 cells/mm3, SD 100 after six months on the current PI based regimens. Two patients had virological blips at 12 months and 18 months on the current PI based regimens but these blips returned to undetectable levels after six more months on the PI-based regimens. There was no statistically significant incidence of viral blip by regimen (P=0.679). So none of the regimens were more likely than others to lead to regimen failure. The patient (male) who had a blip at 12 months (male) had a low level viraemia (VL=708 copies/ml) and the one who had it at 18 months (female) had a high viraemia

(1503 copies/ml), and she admitted to having unprotected sex with her HIV-positive partner at the time. This was an interesting finding but a conclusion was not drawn.

5.3 LIMITATIONS OF THE STUDY

Some limitations were encountered during data collection and analysis that might impact on the generalisability of the study's findings.

Only patients who attended one specific HIV clinic were included in this study. The inclusive criteria specified that the patients' should have been adherent to a PI-based HAART regimen for at least six months. Consequently, the results cannot apply to patients who had been on such treatment regimens for less than six months or who had defaulted. As only the patients receiving treatment at one clinic were included in this study, no records were found of patients who had died while on PI-based HAART regimens.

No data analysis was available of the number of patients who were on PI-based HAART at the participating clinic. A manual count and categorisation was done to identify all patients aged 21 and older who were on PI-based regimens and who had been adherent on their medications for at least 6 months. Although 59 records identified which fit the inclusion criteria, only 35 patients' records were included during analysis due to missing data. This small number of records might influence the validity and reliability of the study's findings.

The literature review revealed several independent variables which could impact the outcome variables of this research, but which could not be addressed during the data analysis because the relevant information was missing from the patients' files. Such missing information included patients' WHO staging of AIDS as well as their height and weight measurements. Changes in WHO staging and in patients' weight might have added some significant measurable findings about the treatment outcomes of PI-based treatment regimens.

The study intended to study CD4 and VL counts at 6, 12 and 18 months' duration of treatment on a specific PI-based HAART regimen. CD4 and VL counts recorded at six months were analysed because it was the month with the least missing data. The inability to evaluate these treatment outcomes after 12 and 18 months' duration of treatment limited the significance of the current study's findings.

The analysis of both CD4 and CD8 changes could provide more accurate information about the CD4 change percentage, but the laboratory was incapable of determining CD8 counts. Laboratory tests should in future establish whether or not patients do indeed show resistance to first line HAART regimens before changing them to second line regimens. Such information was unavailable during the current study, making it impossible to identify 1st line HAART failure attributable to HIV resistance or to the patient's non-adherence to the prescribed regimen.

In the reviewed literature, where some data such as CD4 counts were missing, modelling and regression were used to compute the CD4 trajectory over time. This was beyond the scope of the current study, compounded by the amount of missing data in the respondents' files.

Only information recorded in the patients' files could be accessed and analysed. More information might have been obtained by conducting individual interviews with the 35 patients, but permission was not granted for interviewing patients.

Initially the study aimed to conduct the survey in both Trinidad and Tobago, but no permission could be obtained to repeat the study in Tobago in time to meet the submission of this dissertation. As this study was conducted as part fulfilment of the requirements for a masters in public health degree, funds were limited and the researcher could not afford to take unpaid leave to repeat the study in Tobago.

5.4 RECOMMENDATIONS

The recommendations will be presented according to recommendations pertaining to the HIV services rendered at the participating clinic, and to future research projects focusing on patients on 2nd HAART regimens.

Data recorded by the doctors in the participating HIV clinic should be improved and be more accurate. The patients' height, weight and WHO staging should definitely be included. At every clinic visit patients should be questioned about possible side effects and these answers must be recorded. Regular audits of patients' files should be done and reports compiled and shared with the responsible doctors and other health care professionals at the clinic. A monthly chart of such audits should be clearly displayed. Based on these monthly audits, the number of patients treated at the clinic on specific PI-based HAART regimens and their outcomes at 6, 12, 18 months should be recorded. Records should also be kept of patients who died while on PI-based HAART regimens and the causes of these deaths must be analysed.

Patients who do not keep their clinic appointments should be contacted and assisted to continue with their HAART regimen, if possible. Records of such follow-up actions should be maintained.

In future, the laboratory should become capable of testing both CD4 and CD8 which would be useful in analysing CD4 changes.

More studies need to be done to compare treatment outcomes of the 15 different PI-based HAART regimens. Qualitative analysis should be included by gathering data directly from patients on their experiences of using specific PI-based regimens.

5.5 CONTRIBUTIONS OF THE STUDY

There were previously no data on PI-based HAART efficacy in the SFGH. This research is the first of its kind reported for the SFGH, Trinidad and Tobago.

Identification of all the limitations encountered while gathering the data brings awareness into how to improve the recording system in the department to enable future studies.

5.6 CONCLUDING REMARKS

Some important connections were revealed by the present study such as the higher efficacy of some PI-based regimens and the higher CD4 change percent with lower baseline CD4 quadrant. These however, are findings different from some other studies. Due to the poor quality of data recording and incomplete datasets, a definite conclusion cannot be drawn about the connections established in this study. A further study needs to be carried out, preferably a prospective cohort study in which data quality would be improved and the results would less likely be due to chance than actual significance.

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UNISA university of south africa

UNIVERSITY OF SOUTH AFRICA
Health Studies Higher Degrees Committee
College of Human Sciences
ETHICAL CLEARANCE CERTIFICATE

HSHDC/56/2012

Date of meeting: 23 May 2012 Student No: 3733-506-5

Project Title: A comparison of the effectiveness of protease inhibitor-based highly active anti-retroviral treatment regimens in Trinidad and Tobago.

Researcher: Elohor Ziregbe

Degree: Masters in Public Health (MPH) Code: DIS4986

Supervisor: Prof VJ Ehlers
Qualification: D Litt et Phil
Joint Supervisor: -

DECISION OF COMMITTEE

Approved [√] **Conditionally Approved** [ ]

Prof L Roets
CHAIRPERSON: HEALTH STUDIES HIGHER DEGREES COMMITTEE

Prof MM Moleki
ACTING ACADEMIC CHAIRPERSON: DEPARTMENT OF HEALTH STUDIES

PLEASE QUOTE THE PROJECT NUMBER IN ALL ENQUIRES

Annexure 1: Checklist for data collection from patients' records

Checklist number:

SECTION A: DEMOGRAPHIC AND MEDICAL INFORMATION

1.1 Gender: (a) Male

(b) Female

1.2 Age

21-25	
26-30	
31-35	
36-40	
40-45	
46-50	
51-55	
56-60	
61+	

1.3 Educational level completed:

None	
Primary	
Secondary	
Tertiary (please specify)	

1.4 On second line ARVS at least six months?

(a) Yes (b) No

Questions 1.5 – 1.7 for women only

1.5 Has she ever been pregnant since starting second line ARVs?

(a) Yes

(b) No

1.6. If yes, how many times?

(a) 1

(b) 2

(c) 3

(d) 4

(e) >4 (specify).....

1. 7. Did she stop ARVs during Pregnancy?

(a) Yes

(b) No

1. 8. Has the patient had any other medical conditions apart from HIV?

(a) Yes

(b) No

1.9. If yes to 1.11, tick any from this list

(a) Diabetes

(b) Hypertension

(c) Peptic Ulcer/GERD

(d) Asthma

(e) Epilepsy

(f) Liver disease

(g) Heart disease

(h) Kidney disease

(i) connective tissue disease

(j) previous splenectomy

(k) Cancer (Specify)……

(l) Major Surgery

(m) Acute infection (specify)……..

(n) Other (specify)…….

SECTION B: ANTIRETROVIRAL HISTORY

2.1 Current ARV regimen:

(a) 2a second line

(b) 2b second line

2.2 What was this patients' first line regimen?

(a) Truvada + EFV

(b) Other combinations (Specify from the list following).....

Date started	Drug Combination	Date stopped and why	Any periods of interruption?(explain)

Tenofovir (TDF), Emitricitabine (FTC), Lamivudine (3TC), Stavudine (d4T),Nevirapine (NVP), Efavirenz (EFV), Zidovudine (AZT)

2.3 When exactly was failure of first line suspected by the doctor?

dd/mm/yyyy

2.4 How many months was the patient on the same first line regimen after Failure was suspected ?

(a) < 1month

(b) 1-2 months

(c) 2-3 months

(d) 3 months

(e) > 3months

2.5 Was there any interval of no ARVs being used by this patient before starting second line ARVs?

(a) Yes

(b) No

2.6 If yes to 2.7, how long was this interval?

(a) < 1month

(b) 1-2 months

(c) 2-3 months

(d) 3 months

(e) > 3months

2.7 Mark any of the reason(s) below which may be the cause for changing to second line regimen (Note: more than one reason may be ticked) :

Virologic failure (Increased VL)	
Immunologic failure (decreased CD4)	
Clinical failure	
Drug toxicity	
Others (specify)	

SECTION C: COUNSELLING AND ADHERENCE INFORMATION

3.1 Was the patient adherent to first line ARVs before switching to the 2nd line Regimen ?

(a) Yes

(b) No

3.2 If the response was 'yes' to question 3.1, please indicate how this adherence was determined and the adherence level (if possible).

(a) pill count

(b) pharmacy refill date records

(c) history from patient

(d) Other (specify).....

3.3 Was the patient counselled on adherence before second line ARV initiation?

(a) Yes

(b) No

3.4 If yes to 3.3, how many adherence sessions did the patient attend?

(a) 1

(b) 2

(c) 3

(d) >3

3.5 Pharmacy refill record

Pharmacy refill dates	Number of months of 2nd line ARVs prescribed	Dates when patient returned for refill
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10		
11.		
12.		

3.6. How many appointments has this patient missed at this clinic since starting treatment on second line?

(a) 1

(b) 2

(c) 3

(d) >3

3.7 Did the patient miss any medications since starting second line ARVs?

(a) Yes

(b) No

3.8 If yes, what action did the patient take?

(a) skipped the dose altogether

(b) took the dose late

(c) doubled the dose the next time he took his pills

(d) Borrowed pills from another patient as his/her pills had finished

(e) Other action (specify).....

3.9 Did the patient miss second line medications for any of the following Reasons?

Cause	**Yes**	**No**	**If yes, how many times?**	**How long was he/she off for this reason?**
Felt better				
Clinic was not accessible (too far away)				
No money to go to the clinic				
Lack of food to take with medicines				

Depressed				
Too many pills				
Lack of care/support				
Hospitalised (too ill)				
Did not understand instructions				
Alcohol use				
Forgot				
Ran out of pills				
Side-effects				
Was in public place(fear of stigma)				
Alternative treatment(specify)				
Others (please specify)				

3.10 Since starting taking second line ARVs has the patient visited any other kind of healer? (a) Yes

(b) No

3.11 If yes to 3.10, who? (a) Herbalist

(b) Spiritualist

(c) Pastor/Priest

(d) Imam

(e) Other (specify).....

3.12 What treatment did the other healer recommend?

(a) Herbal medications

(b) Prayers only

(c) Sex with virgin

(d) Healthy diet

(e) Multivitamins

(f) Abstinence

(g) Other (specify).....

SECTION D: SECOND LINE TREATMENT HISTORY

4.1 Date initiated on second line regimen:

dd/mm/yyyy

4.2 Calculated duration of second line ARV treatment in months (at the point in time the data was collected):

6 months	
12 months	
18 months	
24 months or longer	

4.3 CD4 cell count values:

	CD4	CD4/CD8 ratio	CD4%	(dd/mm/yyyy)
Baseline				
6months				

12months				
18months				
24 months				

4.4 Plasma Viral load:

	Value	Date (dd/mm/yyyy)
Baseline		
6months		
12months		
18months		
24 months		

4.5 Clinical Stage:

	Stage	Date (dd/mm/yyyy)
Baseline		
6months		
12months		
18months		
24 months		

4.6 Weight:

	Value	Date (dd/mm/yyyy)
Baseline		
6months		
12months		
18months		
24 months		

4.7 Did the patient have any documented acute illness/ surgery/TB at the time Of the blood tests referred to in questions 4.3 and 4.4?

(a) Yes

(b) No

4.8 If yes to 4.7, was this illness Immune Reconstitution Inflammatory Syndrome?

(a) Yes

(b) No

4.9 What was the presentation of the illness and at what month on second Line treatment?

Presentation	Baseline	6months	12 months	18 months	24 months	Other
Fever						
Rash (specify type of rash)						
Diarrhoea						
Cough/Pneumonia/TB (specify)						
Meningitis						
Others(specify)						

4.10 What other medications/drugs (besides ARVs) were prescribed for this patient since starting second line ARVs? Please write the name of the prescribed drugs in the appropriate block in the table below.

Tick (date started)	Drug	How many times per day?	Duration of use?
	Pain killers		
	Appetite stimulants/vitamins		
	Sleeping pills		
	TB treatment		
	Antibiotics		
	Fungal infection treatment		
	Corticosteroids		
	Interferon		
	Cancer treatment (specify)		
	Others		

4.11 Was the patients regimen switched from 2a to 2b on account of failure on 2a? (a) Yes

(b) No

4.12 If yes to 4.9, what date exactly was this? .....

SECTION E: SIDE EFFECTS

5.1 Has the patient experienced side-effects to the second line ARV regimen?

(a) Yes

(b) No

5.2 If yes to 5.1, tick the side effects below (more than one may be ticked)

Side effects	**Yes**	**No**	**If yes, how many times**	**Treatment/management of each side-effect**
Nausea				
Vomiting				
Diarrhoea				
Headache				
Skin Rash				
Dizziness				
Depression				
Skin or nail discolour				
Anaemia				
Others (please specify)				

5.3 Documented anaemia on second line ARVs?

(a) Yes

(b) No

5.4 What were the Hgb levels and number of months on second line when the tests were done?

	<3mg/dl	4-5mg/dl	6-7mg/dl	8-9mg/dl	>10mg/dl
Baseline					
1month					
2months					
3months					
6months					
12months					
18months					
24months					

5.5 Was the 2b Regimen switched to 2a on account of any side effect?

(a) Yes

(b) No

5.6. If yes to 5.5, Please specify the side effect

Side effects	**Yes**	**No**	**If yes, how many times**	**Treatment/management of each side-effect**
Nausea				
Vomiting				
Diarrhoea				

Headache				
Skin Rash				
Dizziness				
Depression				
Skin or nail discolour				
Anaemia				
Others (please specify)				

5.7 If yes to 5.5, how many months on second line 2b HAART was this?

(a) < 1month

(b) 1 month

(c) 2 months

(d) 3 months

(e) > 3months (specify).....

5.8 Was the side effect resolved after switching 2b to 2a regimen?

(a) Yes

(b) No

5.9 If there was anaemia due to 2b, and 2b was switched to 2a, how long Did the patient continue 2b before switching to 2a?

(a) < 1month

(b) 1 month

(c) 2 months

(d) 3 months

(e) > 3months (specify).....

5.10 Wes there any period of no ARVs taken before switching 2b to 2a?

(a) Yes

(b) No

5.11 What were the Hb levels after switching 2b to 2a and number of months After switching it got to this level?

	<3mg/dl	**4-5mg/dl**	**6-7mg/dl**	**8-9mg/dl**	**>10mg/dl**
1month					
2months					
3months					
6months					
12months					
18months					
24months					

5.12 What other action was taken to correct the anaemia ?

(a) dietary measures

(b) hematinics

(c) blood transfusion

(d) Other (specify)

==========

Annexure 3: Permission letter to the Ministry to conduct the research

c/o Amanda Taylor
United Nations Volunteers
UNDP
42 Brickdam and Un Place
Georgetown
…….2012

The Chairman
Research and Ethics Committee
Ministry of Health
Guyana

Dear Sir/Madam,

PERMISSION TO CONDUCT RESEARCH AT NATIONAL CARE AND TREATMENT CENTER (NCTC).

I am a medical doctor registered with the Ministry Of health of Guyana. I am a registered MPH student at the University of South Africa (UNISA).

I request permission to conduct research at NCTC, Guyana. This research is part of the requirements for completing the MPH (Master's in Public Health) degree at the Department of Health Studies, University of South Africa (Unisa), Pretoria. My Unisa student number is 37335056. Please find attached letter from the Research and Ethics Committee, Department of Health Studies, UNISA, granting ethical clearance for conducting this study.

study such as this will contribute to the existing body of the knowledge about HAART efficacy. No other study could be traced that compared the treatment outcomes of 2a and 2b HAART regimens. Only checklists will be used to collect data from the records of patients on 2a and 2b HAART. The researchers will collect all data personally. The completed checklists will be kept under lock and key. Only the researcher, the study's supervisor and the statistician will have access to the raw data. No patient's name will be recorded on the completed checklist, only a new respondent number. The

researcher will keep a list correlating each respondent number with a specific patient number, in case queries need to be addressed. Only the researcher will have access to this list and it will be locked up in a secure place. After the report has been accepted, this list will destroyed and all completed checklists as well.

No patients and no staff members will be interviewed or asked to complete questionnaires. Consequently data gathering from the patients' records should not impact negatively on the functions of the clinic and should not impact on patients or staff in any manner whatsoever.

The findings of the study will be communicated to your office, to the NCTC and to the healthcare providers at the participating site, after it has been accepted by the University of South Africa.

I shall be very pleased if you could grant me the permission to carry out the study. Should you have any queries, please do not hesitate to contact me or my supervisor on the contact details provided below.

Yours faithfully,

Dr Elohor Ziregbe. (Researcher: +1 868 350 3198)

Prof. VJ Ehlers (Supervisor: 0027 12429 6731)

Annexure 3b: Permission Letter to the Institution to conduct research

c/o Amanda Taylor
United Nations Volunteers
UNDP
42 Brickdam and UN Place
Georgetown
…….2012

The Medical Director,
National Care and treatment Center,
Thomas Street,
Georgetown,
Guyana.
Dear Madam,

PERMISSION TO CONDUCT RESEARCH

I am a medical doctor registered with the Ministry Of health of Guyana. I am also a registered MPH student at the University of South Africa (UNISA). Please find attached letter from the Research and Ethics Committee, Department of Health Studies, UNISA, granting ethical clearance for conducting this study.

I wish to apply for permission to carry out a study to compare the efficacy of two highly active antiretroviral treatment regimens at the National Care and Treatment Center, in Guyana. This is part of the requirements for the completion of my MPH (master's degree in public health).

A study such as this will contribute to the existing body of the knowledge about HAART efficacy. No other study could be traced that compared the treatment outcomes of 2a and 2b HAART regimens. Only checklists will be used to collect data from the records of patients on 2a and 2b HAART. The researchers will collect all data personally. The completed checklists will be kept under lock and key. Only the researcher, the study's supervisor and the statistician will have access to the raw data. No patient's name will be recorded on the completed checklist, only a new respondent number. The researcher will keep a list correlating each respondent number with a specific patient number, in case queries need to be addressed. Only the researcher will have access

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Yours faithfully,

Dr Elohor Ziregbe. (Researcher: +1 868 350 3198)

Prof. VJ Ehlers (Supervisor: 0027 12429 6731)