What Are the Reasons for Switching ART Patients to Second-Line Regimen in Public Healthcare Settings in Gauteng?

A Study Conducted by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program
In collaboration with the
Gauteng Department of Health

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What Are the Reasons for Switching ART Patients to Second-Line Regimen in Public Healthcare Settings in Gauteng?

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Key Words

second-line antiretrovirals (ARVs), compliance, standard treatment guidelines, switch to second-line regimens

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CONTENTS

ABBREVIATIONS AND ACRONYMS

3TC	lamivudine
ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
ARV	antiretroviral
AZT	zidovudine
CHC	Community Health Centre
CI	confidence interval
D4T	stavudine
ddI	didanosine
EFV	efavirenz
HIV	human immunodeficiency virus
LPV/r	lopinavir-boosted ritonavir
MSH	Management Sciences for Health
MSD	Medical Supplies Depot
NVP	nevirapine
OR	odds ratio
PHC	primary healthcare facility
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
STG	standard treatment guideline
STI	sexually transmitted infection
TB	tuberculosis
TDF	tenofovir
USAID	US Agency for International Development
VL	viral load
WHO	World Health Organization

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EXECUTIVE SUMMARY

Introduction

Although almost 1.4 million[1] people were on antiretroviral therapy (ART) in South Africa in December 2010, the estimated ART coverage was only 55 per cent [52–58 per cent][1] in 2011. With 5.6 million [5.4 million–5.8 million] people living with HIV in 2009,[2] the National Department of Health's *National Strategic Plan on HIV, STIs and TB 2012–2016*[3] stated goal to ensure that at least 80 per cent of people who are eligible for HIV treatment receive it has significant financial implications.

The provision of ART in the South African public sectors is based on the use of a limited number of antiretrovirals (ARVs), selected based on their cost/benefit ratio and ease of administration. South African *Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents*,[4] published in 2010, provide standard treatment guidelines (STGs) relevant to the South African context and define the first- and second-line regimens to be prescribed in public healthcare facilities. The number of ARVs available for second-line regimens is limited compared to first-line regimens, and they are also more expensive. In this context, the public health implications of compliance with the guidelines are an important consideration for the patients, for health facilities, and for the health system in general.

A recent analysis of the consumption data from the Gauteng Provincial Medical Supplies Depot (MSD) was used to extrapolate percentages of patients on second- and first-line ART at facilities in 2011. The differences in the percentages of patients on second-line treatment among the facilities raised the question of the rationale for switching patients to second-line regimen in Gauteng Province.

Aims, Objective, Methods

The purpose of the research was to identify the reasons for switching patients from first-line regimens to second-line regimens in the public healthcare setting in Gauteng Province.

The objectives of the study were—

- To assess adherence to guidelines for switching ART patients to second-line regimen
- To document the reasons for switching from first- to second-line regimens
- To identify clinical and other factors contributing to the switch to second line
- To calculate the cost implications of the lack of compliance with approved ART guidelines

This study was an observational descriptive study. Randomly selected medical records for patients over 15 years old on second-line ART regimen attending public healthcare facilities in Gauteng's five districts were reviewed to assess compliance with STGs, document the reasons for switching, and identify factors influencing the switch to second-line regimen.

Key Findings

The key findings from the study are as follows—

- Low level of compliance with the STGs
  Only 49.4 per cent of the patients were switched to the second-line regimen in compliance with guidelines. This low percentage was partly because of lack of systematic adherence assessment (47.4 per cent). The absence of second viral load (VL) was responsible for 32.1 per cent of the non-compliance, implying switching was done without supporting laboratory evidence.

- Various reasons for switching recorded in medical records
  Adverse drug reactions (ADRs) and pregnancy were among some of the recorded reasons for switching, which is not in line with the recommended national guidelines. Forty-five medical records had no stated reasons for switching. Among the patients switched for regimen failure, only 46.7 per cent were switched in compliance with the guidelines; hence, regimen failure was recorded as a reason for switching without supporting evidence.

- Identified factors contributing to the switch
  The district attended by the patients was a contributing factor with higher risk of not being switched in compliance with the guidelines in Ekurhuleni facilities. Patients initiated on tenofovir-based regimens stayed a shorter period on first-line ART before being switched. Within the sample of patients, 75 per cent had been on first line for less than four years prior to the switch.

- Based on the current (2013) government contract prices, 50.6 per cent non-compliance with the guidelines cost an extra R 8.79 millionper year per 10,000 patients on second-line ART.

As the programme ages and the number of patients put on treatment increases dramatically, it is crucial to ensure that only patients with confirmed virological failure and a good record of adherence are switched to second line.

BACKGROUND

Introduction

HIV, AIDS, and tuberculosis (TB) have been recognised as significant contributors to the burden of disease faced by South Africans.[5] With almost 1.4 million[1] people on ART by December 2010, South Africa has the world's largest ART programme. To successfully address HIV and AIDS, the National Department of Health had to increase the number of patients on ART. The National Department of Health's *Annual Report 2011–2012*[6] reported the initiation on ART of 617,147 patients during the financial year 2011/12; this figure represented an increase of 32 per cent compared with the previous financial year, during which 418,677 new patients were initiated.

In 2011, the estimated ART coverage was 55 per cent [52 per cent–58 per cent].[1] The Department of Health's *National Strategic Plan on HIV, STIs and TB 2012–2016*,[3] stated its goal to ensure that at least 80 per cent of people who are eligible for HIV treatment receive it. Strategic Objective 3, Sustaining Health and Wellness, aimed at achieving significant reduction in HIV- and TB-related deaths and disability; this objective shall be accomplished by "universal access to affordable and good quality diagnosis, treatment and care". With 5.6 million [5.4 million–5.8 million] people living with HIV in 2009,[2] the provision of comprehensive treatment and care has significant financial implications, as illustrated by the increased allocations to the Comprehensive HIV and AIDS Grant[7] (R 8.7 billion for 2012/13; R 10.5 billion for 2013/14; R 12.2 billion for 2014/15).

The scaling up of ART in the country has resulted in a dramatic increase in the number of patients receiving ART. The provision of highly active ART allows the patients to live longer hence stay longer on treatment. The length of ART treatment may lead to increased need for second-line ART regimens because of therapeutic failures. In 2012, the annual cost of first-line ART for an adult was R 1,442 (tenofovir, lamivudine, and efavirenz); whilst the annual cost of second-line ART was three times more expensive at R 4,670 (zidovudine, lamivudine, and lopinavir/ritonavir).

The provision of ART in the South African public sectors is based on the use of a limited number of ARVs, determined by their cost and ease of administration. This approach, based on the World Health Organization (WHO) recommendations for public health approach, is similar to that used in other resource-limited settings.[8] The clinical decision-making process is simplified through STGs and standard laboratory monitoring. This approach takes into account the reality of the public healthcare system and the burden of the disease in the country.

To ensure good treatment practices relevant to the South African context, the National Department of Health published the *South African Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents*[4] in 2010. Whereas six different regimens are available in first line, only two regimens are available in second line. The protease inhibitor lopinavir-boosted ritonavir (LPV/r) was part of the two second-line ART regimens. This not only limits the choices of the second-line treatment available for patients, but also implies that guidelines for switching must be adhered to, so as not to compromise available treatment options for patients.

In this context, the public health implications of compliance with the guidelines are an important consideration for the patients, for health facilities, and for the health system in general.

Gauteng Province has the second-largest allocation for Comprehensive HIV and AIDS Grant[7] in South Africa. A recent analysis of consumption data from the Gauteng Provincial MSD was used to extrapolate percentages of patients on second- and first-line ART at facilities in 2011. A deeper analysis per district and per facility highlighted differences in the percentages of patients on second-line treatment among the facilities; some facilities have 0 per cent patients on second line whereas other have more than 20 per cent of their ART patients on second line. The second-line ART being more costly, the percentage of patients switched to second-line ART regimens in the public health institutions has important programmatic and financial implications. The level of compliance with the STGs is of crucial importance to ensure rational use of the available resources.

Literature Review

In their recommendations on when to switch ART,[9] the WHO working groups (Internal WHO ART Guidelines Working Group, ART Guideline drafting group, External ART Peer Review Panel, ART Guideline Review Committee) emphasised the need to avoid premature or unnecessary switching to expensive second-line ART. The protease inhibitors included in the second-line regimens are the cost drivers for second-line ART. The recommendations stated that a switch may be undertaken under the following conditions—

- Where available, use VL to confirm treatment failure.
- Where routinely available, use VL every six months to detect viral replication.
- A persistent VL of greater than 5,000 copies per millilitre confirms treatment failure.
- When VL is not available, use immunological criteria to confirm clinical failure.

In resource-limited settings, the adequate timing for switching is essential for public health programmes. Premature switching has financial and clinical consequences as second-line ART is expensive and the last treatment option for many patients; however, late switching may lead to increased mortality.

Keiser et al.[10] found that patients tend to be switched earlier and at a higher CD4 count in programmes with access to VL monitoring, compared to sites without VL monitoring. Switching patients to second-line regimen based on WHO immunological failure criteria appears to reduce mortality with the greatest benefit in patients switching immediately after immunological failure is diagnosed.[11] Several studies[12] have described the management of switches to second-line ART in Sub-Saharan Africa. However, these studies are based on programmes run by non-governmental organisations or dedicated to clinical research. Although this may be a factor in this study, it still remains to be shown how non-governmental organisations affect the switch in sites where they are operating alongside the public health system in Gauteng Province.

In 2011 the WHO AIDS Medicines and Diagnostics Service[1] sent out a questionnaire to the health ministries of the 97 countries with the highest number of people being treated with ART. This questionnaire set out to measure whether the WHO's recommendations for ART in low- and middle-income countries were being implemented. The assessment also sought to

determine what constituted first- and second-line ART as well as the distribution of treatment regimens in these countries. The report provided data from 66 low- and middle-income countries as of December 2010.

The data were split in two groups, African countries were part of group A (45 countries, n = 5,357,020) where only 3 per cent of adults on ART (n = 142,000) were receiving second-line regimen.

In Cambodia, highly active ART was introduced in 2001, and by the end of March 2009 there were 33,287 patients on ART. By March 2009 it was estimated that 1,145 adults, 3.9 per cent, were already on PI-based regimens,[13] meaning that after eight years, 3.9 per cent of the patients had been switched to second-line ART.

A questionnaire sent out to 24 resource-limited countries in 2006 by the WHO[14] asked respondents to estimate, on the cohort that started receiving first-line treatment in 2006, the percentage of patients that would be switched to second-line regimens annually for the next five years. Ten countries responded, and the results were highly variable. Switching rate for the first year was estimated at 1 per cent to 15 per cent and between 5 per cent and 40 per cent over five years.

Keiser et al.[10] studied the rates of switching to second-line regimens amongst treatment programmes in Africa, Asia, and Latin America. The study included 20,113 patients from 17 treatment programmes in 14 different countries. Rates and time to switching were measured, and results showed that 576 patients (2.9 per cent) switched to second-line treatment regimen. The rate of switching overall was 2.4 per 100 person-years (95 per cent CI: 2.2, 2.6). In countries where there is access to VL monitoring, switching occurred earlier. The reasons for switching were available for 241 (42 per cent) of the 576 patients who were switched. The main reasons for switching were treatment failure (74 per cent) and toxicity (10 per cent), while other reasons accounted for 15 per cent. Orrell et al.[15] followed a cohort of patients from September 2002 to August 2005; among them 1.7 per cent were switched because of drug toxicity. Other reasons included low CD4 count at ART initiation and older age.[11]

The following table[10] shows the characteristics of ART programmes included in the analyses. South Africa is the most represented country with four sites, two in Cape Town and two in Johannesburg. The difference between the rates of switching per 100 person-years between the two facilities in Johannesburg is in line with the actual high variability in percentage of patients on second-line regimen among the healthcare institutions in Gauteng.

Table 1. Characteristics of ART Programmes Included in Analyses

Table 1

Characteristics of antiretroviral treatment programmes included in analyses

Site	Site (Country)	Start of programme	No. of patients (No. switching)	Rate of switching per 100 person-years (95% CI)	Routine HIV-1 viral load testing*	No. of patients with viral load (%)
CEPREF	Abidjan (Côte d'Ivoire)	1999	1,941 (46)	1.6 (1.2–2.2)	No	139 (7%)
1290 ANRS	Dakar (Senegal)	1998	194 (0)	0 (0–3.7)	Yes	153 (79%)
AMPATH	Eldoret (Kenya)	2002	3,229 (106)	5.0 (4.1–6.0)	No	0
AMU	Kampala (Uganda)	2002	84 (3)	2.7 (0.9–8.2)	Yes	83 (99%)
Lighthouse	Lilongwe (Malawi)	2000	4,082 (9)	0.2 (0.1–0.3)	No	0
Connaught	Harare (Zimbabwe)	2002	707 (31)	3.5 (2.5–5.0)	No	0
Gugulethu	Cape Town (South Africa)	2002	1,243 (23)	1.8 (1.2–2.6)	Yes	1106 (89%)
Khayelitsha	Cape Town, (South Africa)	2001	1,527 (45)	2.4 (1.8–3.2)	Yes	1444 (95%)
Themba Lethu	Johannesburg, (South Africa)	1999	1,874 (97)	6.5 (5.3–7.9)	Yes	1127 (60%)
PHRU	Soweto (South Africa)	2004	439 (2)	0.8 (0.2–3.3)	Yes	387 (88%)
Morocco	Casablanca (Morocco)	1999	231 (8)	2.5 (1.3–5.0)	Yes	136 (59%)
MTCT-Plus	Several[&]	2003	1,455 (22)	1.7 (1.1–2.5)	No	0
PUMA	Buenos Aires (Argentina)	2003	136 (6)	5.2 (2.3–11.5)	Yes	102 (75%)
SOBRHIV	Porto Alegre (Brazil)	1996	349 (7)	0.8 (0.4–1.7)	Yes	289 (83%)
RIOHIV	Rio de Janeiro (Brazil)	1996	292 (45)	5.7 (4.3–7.6)	Yes	183 (63%)
YRG Care	Chennai (India)	1996	2,114 (122)	3.2 (2.7–3.8)	No	154 (7%)
HIV-NAT	Bangkok (Thailand)	2003	216 (4)	1.0 (0.4–2.6)	No	0
Total			20,113 (576)	2.4 (2.2–2.6)	10/17	5303 (26%)

See appendix for further details on participating sites

[&]Network including sites in South Africa, Zambia, Kenya, Rwanda, Uganda, Ivory Coast, Thailand

*Routine viral load monitoring was defined as at least one measurement between 3 and 9 months after starting ART, in at least 50% of patients

The 2010 South African ART guidelines stated that a switch to second-line ART regimen may be done provided that there was evidence of virological failure (VL > 1,000 copies/millilitre on two occasions) despite intensive adherence counselling. The decision must be supported by biologic measurement to detect and confirm virological failure after confirming that a patient is adherent to his or her treatment regimen. The available literature did not answer the question of the level of compliance with the guidelines for switching patients to second-line ART regimens in the public health institutions in South Africa. Although there is some literature on the percentages of patients in second-line regimens in resource-limited settings, very few studies explored all the possible reasons that may have resulted in the switch to second line.

Because the number of patients on second-line regimens has strong clinical and financial consequences on the Comprehensive HIV and AIDS Care and Treatment programme, this study was undertaken to identify the reasons behind the switch from first-line to second-line ART regimen in Gauteng Province ART sites. The findings will assist in monitoring the usage of LPV/r and inform STGs.

This research report presents the findings on the level of compliance to guidelines for switching patients to second-line ART within the public health care facilities in Gauteng Province.

Research Statements

Purpose

The purpose of the research was to identify the reasons for switching patients from first-line regimens to second-line regimens and to understand the rationale for switching patients in the public healthcare setting in Gauteng Province, South Africa.

Objectives

The objectives of the study were—

- To assess adherence to guidelines for switching ART patients to second-line regimen
- To document the reasons for switching from first- to second-line regimens
- To identify clinical and other factors contributing to the switch to second line
- To calculate the cost implications of lack of compliance with ART guidelines

Outline of Report

The study and research questions are introduced in the background section where the available literature relevant to the research question is then presented. The topics reviewed include the expected percentage of patients on second-line regimens as the HIV/AIDS programmes age and the reasons for switching patients to second-line regimens. The next chapter, "Methodology", outlines the methods used for the study, such as study population, sampling, data collection, and data analysis.

The findings and results of the study are presented in the results chapter and then discussed in the discussion section where the connection is established with the research statements and the literature review.

The final chapter, conclusions and recommendations, brings all the study's findings together as the basis for recommendations on compliance with STGs for switching patients to second-line ART.

Dissemination of Report

The results from the study will be reported to the Gauteng Department of Health and to SIAPS, a technical assistance programme funded by USAID and implemented by MSH.

METHODOLOGY

Study Design

This study was an observational descriptive study. Randomly selected medical records for patients over 15 years old on second-line ART regimen attending public healthcare facilities in Gauteng's five districts were reviewed to assess compliance with STGs, document the reasons for switching regimens, and identify factors influencing the switch to second-line regimen.

Study Setting

The study was conducted in public healthcare institutions providing ART for outpatients in Gauteng Province, South Africa. The public healthcare institutions included primary healthcare facilities (PHCs), district hospitals, regional hospitals, and tertiary hospitals within Johannesburg district, Ekurhuleni district, Sedibeng district, Tshwane district, and West Rand district.

Study Population

The study population was all patients 15 years and older on second-line ART regimen attending public healthcare facilities in Gauteng Province.

Sample

Only patients' records that met the following study criteria were considered—

- Inclusion criteria:
  - Patients aged 15 years or older
  - Patients on second-line ART regimen for a minimum of one month

- Exclusion criteria:
  - Patients on salvage therapy regimen containing LPV/r
  - Patients on first-line therapy
  - Patients 14 years or younger

Sample Size

As mentioned in the literature review, a study found that 74 per cent of patients in the cohort were switched as a result of treatment failure. Thus, it was expected that a similar proportion of patients should be switched for that reason in Gauteng Province. A sample size of 312 medical records was required to detect an increase in adherence from 74 per cent to 80 per cent at a one-sided significance level of 5 per cent and a power of 80 per cent.

Sampling Method

Stratified random sampling was used to select the facilities where patients' medical records were reviewed.

The sampling frame was a list of facilities that received second-line therapy medicines from the MSD. An analysis of the MSD's consumption data for ARVs over the calendar year 2011 indicated that 64 healthcare facilities received LPV/r tablets from the Gauteng MSD during that period. Steve Biko Academic Hospital was excluded from the list of facilities because ARVs are provided only to inpatients during their hospitalisation.

The 64 facilities were stratified according to whether they had a low (less than 6 per cent), medium (6 per cent to 11 per cent), or high (equal or greater than 12 per cent) proportion of patients on second-line therapy. All the facilities meeting this criterion were allocated a number based on alphabetical ranking of clinics. A web-based random number generator (www.randomizer.org) was used to select 50 per cent of the facilities per strata to be included in the study. If the total number of facilities in the strata was an odd number, the number of facilities selected was rounded up.

The number of facilities selected per stratum is detailed in table 2.

Table 2. Number of Facilities Selected per Stratum

	Low (<6%)	Medium (≥6% to <12%)	High (≥12%)
Total number of institutions	31	19	14
Number of institutions selected	16	10	7

The names of the facilities selected are provided in Appendix A.

Based on the total quantity of LPV/r supplied by MSD in the province, an estimated 19,000 patients were on second-line ART regimens in Gauteng in 2011. Table 3 describes how consumption information from the MSD was used to calculate the number and percentage of patients on second-line ART regimen at facilities.

Table 3. Calculation of the Number and Percentage of Patients on Second-Line ART Regimen

Calculation	Information obtained
Quantity of LPV/r 200/50 mg over year / 12 = Q	Number of patients on second line
Sum of quantities of EFV 600 mg, NVP 200 mg, and LPV/r 200/50 mg over year / 12 = Σ	Number of patients on first and second line
(Q*100) / Σ	Percentage of patients on second line

In 2011, an estimated 14,000 patients were on second-line ART regimens attending Gauteng healthcare facilities directly supplied by MSD, namely hospitals, community health centres, and large clinics.

MSD also supplied ARVs to district regional pharmacies that function as sub-depots for the clinics in their respective district. The lack of computerised information systems made it difficult to track the supply of ARVs from the district regional pharmacies to these clinics. For practical reasons, the study population did not account for the patients attending PHCs receiving ARVs from the district regional pharmacies.

The distribution of those patients within each of the strata is shown in table 4. The number of medical records to be selected from each stratum was based on the proportion of all patients within that stratum.

Table 4. Calculation of the Sample Split per Stratum

	Low (<6%)	Medium (≥6% to <12%)	High (≥12%)	Total
Estimated number of patients	2,394	4,135	7,804	14,334
Weighting percentage	17	29	54	100
Sample split	53	90	168	312

The overall sample of medical records was stratified according to the indicated weighting (table 4) for each stratum. All patients receiving second-line ART were included in the sample frame of each healthcare facility. All patients meeting the inclusion criteria were allocated a number based on alphabetical ranking of their last name. Medical records to be included in the study were then randomly selected from each facility. The numbers of study participants per healthcare facility are provided in Appendix B.

Data Collection

The data collection happened in two phases.

First, for each healthcare facility selected, a list of all eligible patients (last name of all patients on second-line ART regimen meeting the inclusion criteria) was established. An identification number constructed using the last name of the patient was allocated.

The specified sample of patients was randomly selected from the list constructed in each stratum. The data collectors reviewed each patient's medical record, and necessary information was recorded according to the format provided. A structured questionnaire was used to collect quantitative data of each selected participant (Appendix C).

Because of the clinical knowledge needed to review medical records, the review was conducted by pharmacists who had received training on the extraction of data from the medical record and on the use of the questionnaire.

Training was conducted the day prior to the first field visit; it comprised a presentation, practice on data extraction from medical record, and a user manual.

Eleven data collectors conducted the data collection.

Constraints

The list of patients on second-line ART regimen could not be obtained prior to the data collection in Hillbrow Community Health Centre (CHC); because no filing system was available to draw the list on site, the data collectors used a convenient sampling.

At Dr. George Mukhari Hospital, the sample of medical file numbers randomly selected from the list of patients on second-line regimen could not be adhered to because of the lack of systematic filing. Hence, convenience sampling was also used at this facility.

One facility, Diepsloot clinic, is under Johannesburg Metro authority. Diepsloot was in the "low stratum" with four files to be reviewed. Johannesburg local government requested the submission of an application for approval to conduct research in local government facilities. Because only one facility from Johannesburg local government was selected and due to time constraint, it was decided to collect an extra file in four clinics in the same low stratum from local government in Ekurhuleni and not to conduct data collection in Diepsloot clinic. This is not expected to have any significant influence on the results.

Data Collection Tool

Data were extracted from the medical records using a tool specially developed for the study. The tool (Appendix C) allowed collection of the following data elements—

- Adherence to South African guidelines for the management of HIV/ AIDS
  - Per level of care
  - Per district
  - Per prescriber level

- Reason for switching
  - Per level of care
  - Per district
  - Per prescriber level

- Number of months between ART initiation and switch to second line
  - Per CD4 count at ART initiation
  - Per first-line regimen at ART initiation

- Availability of biologic measurement of treatment failure (VL monitoring and CD4) in facility

Data Management and Data Analysis

To prevent undue access, loss, or tampering, the questionnaires from the medical records review are stored in a secure place at the SIAPS office in Pretoria for a period of three years after publication of the findings.

Data were captured with data verification conducted by an independent person to check for accuracy and inconsistencies.

Weighting Process

The weighting process considered the stratification sampling procedure applied in selecting the sample. In addition, the probability of selecting individual records within each stratum was considered. Individual weights were computed as the inverse of the individual probability of being selected within the defined stratum.

For instance, if in the stratum *i* the population was of size N_i and the sample size relating to stratum *i* was n_i, then the probability of selecting an individual from this stratum is n_i/N_i. The weight relating to this individual is therefore N_i/n_i. In general, a weight of w_j for the *j*th patient means *j*th patient represents w_j patients in the population from which the sample was taken. The following example illustrates the computation of individual weights of patients in Hillbrow CHC classified in high stratum: 22 patients of a total 173 gives 22/173 as the probability of being selected. The probability of selecting a patient in Hillbrow CHC and in stratum high is then calculated by multiplying the probability of being selected in Hillbrow CHC with the probability of being in the stratum high. The inverse of resultant probability gives the respective individual weight.

The weighting process took into consideration the strata classification as low (<6 per cent), medium (6 per cent to 11 per cent) and high (≥12 per cent) in terms of the estimated number of patients. Based on this classification of 323 patients, 173 were classified as high, 70 as low, and 80 as medium. Thus, the probability of being in stratum high is 0.484, in medium stratum is 0.297, and in low stratum is 0.219.

The estimates provided in this analysis are all weighted to eliminate bias and are therefore considered to be the appropriate estimates. Where adequate information was available, 95 per cent confidence intervals (95% CI) for the estimates were computed. The results tables provided contain the sample used in estimating the parameter and actual frequency in each of the categories.

Generating New Variables

Various new variables were generated based on the following criteria—

- Patient's age in years
  - The patient's age in years was generated as (date of data collection − date of birth) / 364. The 364 days are assumed to constitute a year.
  - Two age groups were generated as (a) patients 15 to 34 years of age and (b) patients 35 years and older.

- Number of months on first line and second line

  - The number of months on first-line ART regimen was generated as (date of switch − date of first-line ART initiation) / 30. The 30 days are assumed to constitute a month.
  - The number of months on second-line regimen was generated as (date of data collection − date of switch) / 30.
  - Numbers of months were later grouped into 11 groups.

- Compliance with STGs
  - A new variable relating to compliance or non-compliance with STGs was generated based on the following criteria.
  - Considered compliance if
    - latest VL prior to switch > 1,000 copies per mL

    AND
    - second-latest VL prior to switch > 1,000 copies per mL

    AND
    - adherence assessment = Yes

More than one possible reason exists for non-compliance; however, the following were considered—

- Latest VL prior to switch NOT > 1,000 (A)
- Second-latest VL prior to switch NOT > 1,000 (B)
- Second-latest VL prior to switch absent (C)
- Adherence assessment = No (D)
- A and B
- A and C
- A and D
- Other combinations of A, B, C, and D

Notes:
- A, B, C, and D are proportions of non-compliance.
- One patient from non-compliance can be represented in A, B, C, and D.

Descriptive and Inferential Statistics

Data that involved categories were tabulated; the number of patients was given in each category with the proportion in percentage and 95 per cent confidence intervals. Comparing two categories of a particular variable using confidence interval was possible. Where the intervals did not overlap, the two categories were considered to be significantly different. Otherwise, they were not significant at 5 per cent significance level.

For variables that were of a continuous nature (quantitative, such as age), summary statistics that consist of measures of location, measures of dispersion, and level of skewness were provided. The skewness value indicates the nature of distribution of the data. Values closer to zero indicate the distribution to be symmetric (normal), negative values indicate negatively skewed, and positive values indicate positively skewed. The mean was used as the measure of central location for most variables. Median was, however, used for heavily skewed data.

Chi-square test statistics and P-values were provided for testing the degree of association between the categories that were of a qualitative nature.

Ethical and Legal Considerations

The present study received ethical approval from the Research Ethics Committee of Pharma-Ethics. Permission to conduct the study in Gauteng public healthcare facilities was received from the Gauteng Department of Health. Ethical clearance was granted by the Ekurhuleni Ethics Research Committee to conduct research in Ekurhuleni District.

In accordance with ethical requirements, approval was sought and obtained from facility management to access all facilities (Appendixes D, E, F, and G).

RESULTS

A total of 326 medical records were reviewed. However, 3 medical records were excluded from the analysis because they did not meet the selection criteria relating to patient age.

The following abbreviated names of the ARVs were used in this section: efavirenz = EFV; lamivudine = 3TC; lopinavir-boosted ritonavir = LPV/r; nevirapine = NVP; stavudine = D4T; tenofovir = TDF; zidovudine = AZT.

Characteristics of the Study Population

Demographic and Social Characteristics

Females accounted for 68.5 per cent (n = 224) of the medical records sampled. The study sample was categorised in two age groups; namely, 15 to 34 years of age and 35 years and older. The majority of the population, 68.2 per cent (n = 221) was 35 years and older (table 5). This trend was expected as the study sample is already on second-line ART.

Table 5. Demographic Characteristics of the Study Sample

Assessment criteria	Gender (N = 321)	
	Male	Female
Frequency	97	224
Percentage	31.5	68.5
95% CI	22.6–42.0	58.0–77.4
	Age group (N = 320)	
	15–34 years	35+ years
Frequency	99	221
Percentage	31.8	68.2
95% CI	26.8–37.3	62.7–73.2

With 148 files, Johannesburg district has the largest sample of the five districts (table 6). This can be explained by the presence of Helen Joseph Hospital, with a sample of 85 files, in this district. In terms of the number of files per district, Ekurhuleni is second with 61, followed by West Rand and Tshwane. Sedibeng district has the smallest sample (10).

Table 6. Distribution by District

Assessment criteria	District (N = 323)				
	Johannesburg	Ekurhuleni	Sedibeng	Tshwane	West Rand
Frequency	148	61	10	49	55
Percentage	31.5	25.9	5.2	16.3	21.1
95% CI	19.5–46.7	12.0–47.2	1.5–16.1	6.8–34.2	5.2–56.7

Similarly, the facility type group *hospital* having the highest (205) number of medical records can be explained by the inclusion of Helen Joseph Hospital in this group (table 7).

Table 7. Distribution by Type of Facility

Assessment criteria	Facility type (N = 319)		
	Hospital	CHC	PHC
Frequency	205	49	65
Percentage	55.5	18.8	25.8
95% CI	10.7–92.8	2.2–70.1	3.0–79.4

Current Treatment Regimens

Because of the skewness of the data, median is preferred as the measure of central location.

Among the study sample 48.5 per cent (n = 153) of the patients were on TDF, 3TC, and LPV/r as current second-line regimen. The second highest percentage was 27.4 per cent (n = 85) for AZT-containing regimen, while D4T-containing regimen had the lowest percentage with 5.7 per cent (n = 30) (table 8).

Table 8. Current ART Regimen

	Current ART regimen (N = 321)			
Assessment criteria	TDF + 3TC + LPV/r	AZT + 3TC + LPV/r	D4T + 3TC + LPV/r	Others (including AZT + DDI + LPV/r)
Frequency	153	85	30	53
Percentage	48.5	27.4	5.7	18.4
95% CI	35.8–61.5	17.4–40.2	2.0–15.1	10.9–29.3

Length of Time on Current Regimen

Patients had been on second-line ART for a minimum of 0.2 years and a maximum of 8.6 years at the time of data collection. The median number of years for the duration of second-line ART was 1.7 years (table 9).

Table 9. Summary Statistics on Duration of Second-Line ART

Duration on second-line ART	N	Mean	Standard deviation	Median	Min	Max	Skewness
Months	293	24.1	17.66	20.2	1.5	103.7	1.54
Years	293	2.0	1.47	1.7	0.2	8.6	1.54

Length of Time on Current Regimen by Gender and Age Group

There was no notable difference between male and female with regard to medium, minimum, and maximum number of months on second line. The age group 15–34 had a median of 17.8 (min = 1.6; max = 77.8) months whereas the age group over 35 showed a higher median of 22.2 (min = 1.5; max = 103.7) months (table 10).

Table 10. Summary Statistics on Duration of Second-Line ART in Months, by Gender and Age Group

Duration on second-line ART		N	Mean	Standard deviation	Median	Min	Max	Skewness
Gender	Male	90	22.2	16.65	19.0	1.5	96.9	1.58
	Female	202	25.3	18.07	20.3	1.6	103.7	1.52
Age group	15–34	86	20.3	13.39	17.8	1.6	77.8	1.47
	35+	205	26.1	18.85	22.2	1.5	103.7	1.44

Length of Time on Current Regimen by Districts

Patients attending Sedibeng district facilities had been a median of 31.1 (min = 11.8; max = 54.7) months on second line, the highest median across the districts. The lowest median value was in West Rand with 17.8 (min = 2.6; max = 67.5) months (table 11).
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Table 11. Summary Statistics on Duration of Second-Line ART in Months by District

District	N	Mean	Standard deviation	Median	Min	Max	Skewness
Johannesburg	133	28.4	22.39	20.2	1.5	103.7	1.27
Ekurhuleni	57	20.4	16.03	18.4	1.6	83.4	1.65
Sedibeng	9	28.6	14.50	31.1	11.8	54.7	0.23
Tshwane	47	22.8	12.82	20.9	3.1	57.4	1.04
West Rand	47	21.8	13.50	17.8	2.6	67.5	1.23

Length of Time on Current Regimen by Type of Facility

The patients at hospitals had been a median of 21.7 (min = 1.5; max = 103.7) months on second line whereas the ones at CHCs had been a median of 14 (min = 2.2; max = 83.4) months (table 12).

Table 12. Summary Statistics on Duration of Second-Line ART in Months by Type of Facility

Facility	N	Mean	Standard deviation	Median	Min	Max	Skewness
Hospital	188	24.6	17.28	21.7	1.5	103.7	1.46
CHC	47	19.7	15.18	14.0	2.2	83.4	1.73
PHC	54	24.9	19.84	18.3	1.6	92.9	1.76

Who Switched the Patients?

The majority (87.2 per cent, n = 280) of the patients were switched to second-line regimens by medical doctors (table 13). Among the 26 patients switched by professional nurses, 13

attended a PHC facility and 9 a CHC. None of the patients in Tshwane district were switched by a professional nurse.

Table 13. Qualification of the Prescriber Who Prescribed the Switch to Second-Line ART

	Qualification of prescriber (N = 306)	
Assessment criteria	**Medical doctor**	**Professional nurse**
Frequency	280	26
Percentage	87.2	12.8
95% CI	62.3–96.5	3.5–37.7

ART Regimen at Initiation

The circumstances around the switch to second line, the regimen at initiation, and duration on first-line ART were studied to better understand the switch.

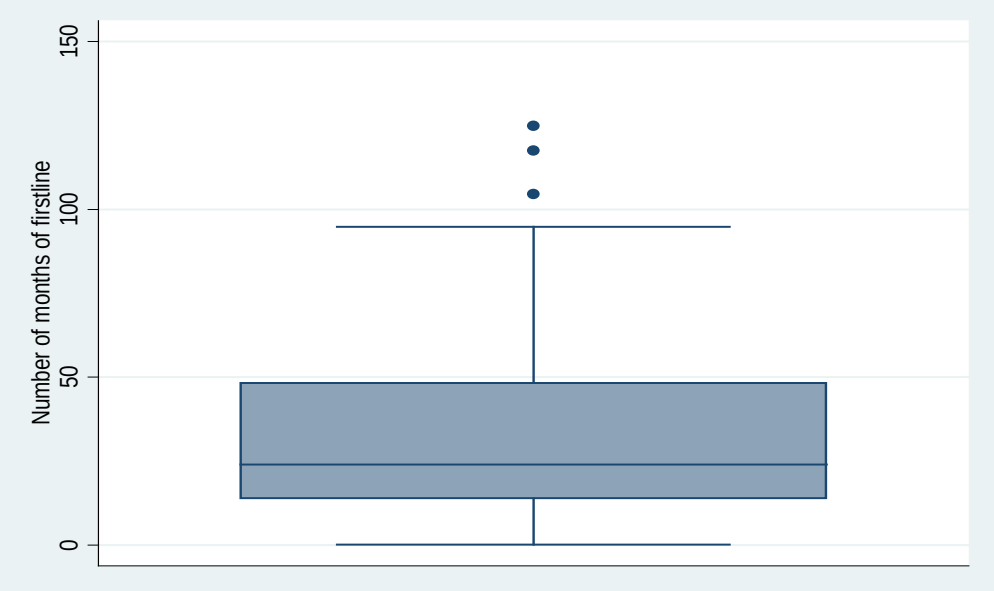
Length of Time on First-Line Regimen

The median number of years on first-line regimen before being switched to second line was two (min = 0.0; max = 10.4; table 14).

Table 14. Summary Statistics on Duration of First-Line ART Regimen

Duration on first-line ART	N	Mean	Standard deviation	Median	Min	Max	Skewness
Months	253	30.6	23.18	24.0	0.0	124.9	1.35
Years	253	2.6	1.93	2.0	0.0	10.4	1.35

Seventy-five percent of the patients remained on first-line regimen for less than four years (lower quartile = 12.38 months; upper quartile = 45.42 months), as illustrated by the boxplot on the number of months on first line (figure 1).



Note: Mean = 30.13; Median = 24.07; Minimum = 0.0333; Maximum = 124.9; Range = 124.8; Lower quartile = 12.38; Upper quartile = 45.42; Standard deviation = 23.03; Variance = 530.2.

Figure 1: Boxplot on number of months on first line

Length of Time on First Line by Gender and Age Group

With a median of 29.2 (min = 0.7; max = 104.5), men appeared to stay longer on first line compared to women (20.3; min = 0.0; max = 124.9) (table 15). The minimum number of months for the female group was 0.0, meaning that some women were not initiated on first-line but on second-line regimen whereas this was not the case for men.

Table 15. Summary Statistics on Duration of First-Line ART Regimen in Months by Gender and Age Group

Duration on first-line ART		N	Mean	Standard deviation	Median	Min	Max	Skewness
Gender	Male	75	32.8	22.39	29.2	0.7	104.5	0.90
	Female	177	29.6	23.73	20.3	0.0	124.9	1.56
Age group	15–34	74	25.9	21.94	20.1	0.0	104.5	1.69
	35+	178	32.7	23.53	27.2	0.4	124.9	1.24

Length of Time on First Line by District

With a median of 42.9 (min = 12.7; max = 53.0) months on first line, Sedibeng district had the highest median, although the maximum number of months was the lowest of the five districts (table 16).

Table 16. Summary Statistics on Duration of First-Line ART Regimen in Months by District

District	N	Mean	Standard deviation	Median	Min	Max	Skewness
Johannesburg	120	31.3	27.92	20.7	0.0	124.9	1.54
Ekurhuleni	49	29.4	22.39	21.5	0.5	104.5	1.53
Sedibeng	9	37.7	16.07	42.9	12.7	53.0	−0.43
Tshwane	33	30.2	19.73	31.4	0.7	94.8	0.42
West Rand	42	29.2	19.13	23.3	0.4	78.6	0.39

Length of Time on First Line by Type of Facility

Patients attending CHCs stayed on first line a median of 20.3 months (min = 1.1; max = 62.8) while the population treated at hospitals or PHCs stayed longer on first line with a median of 26.6 (min = 0.4; max = 124.9) months (table 17).

Table 17. Summary Statistics on Duration of First-Line ART Regimen in Months by Type of Facility

Facility type	N	Mean	Standard deviation	Median	Min	Max	Skewness
Hospital	162	29.3	21.23	24.0	0.0	104.5	1.10
CHC	40	27.2	17.98	20.3	1.1	62.8	0.39
PHC	48	38.7	30.79	26.6	0.4	124.9	1.22

Length of Time on First-Line and Qualification of Prescriber for the Switch

There was no significant association (p-value = 0.813) between the number of months on first line and the qualification of the prescriber who prescribed the switch to second-line ART (table 18).

Table 18. Qualification of Prescriber and Number of Months on First-Line ART

Number of months on first-line ART	Qualification of prescriber			
	Doctor (N = 226)		Professional nurse (N = 19)	
	Frequency	%	Frequency	%
<1 month	8	2.5	1	2.2
1 to 6 months	16	6.3	1	8.2
7 to 12 months	38	15.3	1	10.4
13 to 24 months	58	29.1	4	17.6
25 to 36 months	36	15.3	3	14.1
37 to 48 months	22	8.6	2	11.1
49+ months	48	22.8	7	36.4

Test statistic: Chi-square = 3.10; p-value = 0.813.

Regimen at Initiation by Gender and Age Group

A total of 67 men were on EFV-containing regimens, whereas only 14 were on NVP-containing regimens. The same trend was true for women but to a lower extent, with 145 women on EFV-containing regimens and 45 on NVP-containing regimens. Among the age group 15–34 years, 57 patients were on EFV and 27 on NVP. In the 35 years and over group, the frequencies were 152 for EFV-containing regimens and 32 for NVP. The relationships between the regimen at initiation and gender and age group were tested for association but showed no significant association with p-value = 0.253 (table 19) and p-value = 0.125 (table 20), respectively.

Table 19. ART Regimen at Initiation by Gender

ART regimen at initiation (N = 321)	Total			Male			Female		
	Freq	%	95% CI	Freq	%	95% CI	Freq	%	95% CI
AZT+3TC+EFV	18	8.7	3.4–20.3	6	12.1	6.2–22.2	12	7.1	1.8–24.6
D4T+3TC+EFV	158	41.8	30.4–54.2	49	51.8	39.6–63.8	109	37.3	23.4–53.6
TDF+3TC+EFV	34	11.6	8.2–16.2	12	10.0	3.8–23.7	22	12.4	8.5–17.7
AZT+3TC+NVP	10	2.6	1.1–6.1	2	1.1	0.2–7.4	8	3.3	1.3–8.2
D4T+3TC+NVP	40	10.5	4.8–21.6	11	8.5	3.5–19.4	29	11.4	5.1–23.7
TDF+3TC+NVP	9	3.8	0.8–15.4	1	1.1	0.1–14.8	8	5.0	1.2–19.0
Other regimen	52	21.0	9.3–40.8	16	15.4	9.2–24.6	36	23.5	8.4–50.6

Test statistic: Chi-square = 12.69; p-value = 0.253.

Table 20. ART Regimen at Initiation by Age Group

ART regimen at initiation (N = 320)	15–34 years			35+ years		
	Freq	%	95% CI	Freq	%	95% CI
AZT+3TC+EFV	3	3.4	0.7–15.5	13	9.5	3.0–26.1
D4T+3TC+EFV	38	33.0	20.3–48.7	121	47.4	34.0–61.2
TDF+3TC+EFV	16	13.5	10.4–17.4	18	10.8	6.8–16.9
AZT+3TC+NVP	5	4.9	2.2–10.7	5	1.6	0.4–6.3
D4T+3TC+NVP	20	18.3	7.7–37.5	20	7.0	3.5–13.6
TDF+3TC+NVP	2	4.4	0.4–33.7	7	3.5	0.6–19.6
Other regimen	15	22.5	7.5–50.8	37	20.1	9.5–37.5

Test statistic: Chi-square = 18.76; p-value = 0.125.

Regimen at Initiation by Type of Facility

The association between regimen at initiation and type of facility was significant with p-value equal to 0.036 (table 21). In hospitals, 51.6 per cent (n = 118) of patients were initiated on a regimen containing D4T, 3TC, and EFV. In CHCs, 31.9 per cent (n = 17) of the patients were initiated on this regimen. At PHC level, the highest percentage of patients (42.8 per cent, n = 18) were initiated on regimens other than the ones listed in the guidelines. D4T-containing regimens constituted the majority of regimens at initiation with 139 files at hospital, 26 at CHC, and 32 at PHC compared to regimens containing AZT or TDF. Note that patients may have been initiated in another facility than the one where the data collection took place.

Across the three types of facilities—hospital, CHC and PHC—the majority of the study group had been initiated on EFV-containing regimens (147, 25, and 39, respectively) compared to NVP-containing regimens (30, 19, and 8, respectively).

Table 21. ART Regimen at Initiation by Type of Facility

ART regimen at initiation (N = 319)	Hospital			CHC			PHC		
	Freq	%	95% CI	Freq	%	95% CI	Freq	%	95% CI
AZT+3TC+EFV	12	10.0	5.4–17.6	4	15.8	2.5–57.9	2	1.3	0.2–7.0
D4T+3TC+EFV	115	51.6	37.8–65.2	17	31.9	22.5–42.9	27	33.6	28.0–39.6
TDF+3TC+EFV	20	11.4	4.8–24.5	4	10.6	3.3–29.0	10	13.7	6.6–26.1
AZT+3TC+NVP	4	1.7	1.4–2.2	5	8.4	3.0–21.1	1	0.5	0.1–4.9
D4T+3TC+NVP	24	10.3	4.6–21.6	9	16.2	3.9–48.2	5	2.6	0.3–18.2
TDF+3TC+NVP	2	1.3	0.6–3.0	5	9.2	1.3–44.3	2	5.5	0.6–37.6
Other regimen	28	13.7	8.6–21.2	5	8.0	5.3–12.0	18	42.8	24.1–63.8

Test statistic: Chi-square = 68.76; p-value = 0.036.

Reported Co-morbidity, TB Co-infection, and Pregnancy at the Time of the Switch

The presence of pregnancy and/ or co-morbidity at the time of the switch was assessed to gain insight into the context of the switch at patient level.

Co-morbidity

In the majority of the facilities, the ARV clinic and ARV pharmacies are not integrated in the main clinic. In these instances, the patient has more than one file. It is crucial to highlight that other chronic medications were seldom recorded in ARV patients' files. Hence, the frequencies and percentages listed in table 22 may not be a complete and true reflection of the co-morbidity situation. The percentage of patients with co-morbidity was probably higher.

Table 22. Co-morbidity at the Time of the Switch

Assessment criteria	Category	Frequency	%	95% CI
Mental health condition (N = 309)	No	295	95.3	83.9–98.7
	Yes	14	4.8	1.3–16.1
Liverfailure (N = 310)	No	304	98.6	92.6–99.8
	Yes	6	1.4	0.2–7.4
Renal failure (N = 312)	No	308	99.4	98.1–99.8
	Yes	4	0.6	0.2–1.9
Diabetes (N = 306)	No	305	99.9	99.4–100.0
	Yes	1	0.1	0.0–0.6
High hlood pressure (N = 306)	No	285	95.0	91.9–96.9
	Yes	21	5.0	3.1–8.1

TB Co-infection

Although 30 to 40 per cent of HIV patients will develop TB in their lifetime, the lack of data related to TB co-infection in the patients files reviewed does not allow for any inference (table 23).

Table 23. TB Co-infection at the Time of the Switch

Assessment criteria	Category	Frequency	%	95% CI
TB co-infection (N = 307)	No	275	92.0	78.6–97.3
	Yes	32	8.0	2.7–21.4
TB treatment (N = 15)	New case	14	89.3	—
	Retreatment	1	10.7	—
	Multi-drug resistant	0	0.0	—
	Extensively drug resistant	0	0.0	—

— Not available.

Pregnancy

Only 22.3 per cent of female patients were recorded as being pregnant at the time of the switch (table 24).

Table 24. Pregnancy at the Time of the Switch

Assessment criteria	Pregnancy at the time of the switch (N = 198)	
	No	Yes
Frequency	161	37
Percentage	77.7	22.3
95% CI	53.7–91.3	8.7–46.3

Unfortunately, the poor quality of the data in these categories makes it difficult to investigate further any association between the switch to second-line ART and pregnancy, TB, or co-morbidity.

Adherence

Adherence is a very important component in the management of HIV and AIDS. The guidelines state that an adherence assessment should be carried out prior to switching patients to second line and, if necessary, adherence counselling be provided. No recommendations are made in the guidelines in relation with the kind of adherence counselling (individually or group counselling).

Figure 2 shows that adherence was assessed for only 57.2 per cent (n = 173) of the patients on second line. Once assessed, 89.6 per cent (n = 151) of the patients received adherence counselling either individually (70.4 per cent, n =111) or in group counselling (29.6 per cent, n = 39). It was, however, difficult to establish how many of the patients who did not received counselling (10.4 per cent, n = 19) needed counselling.

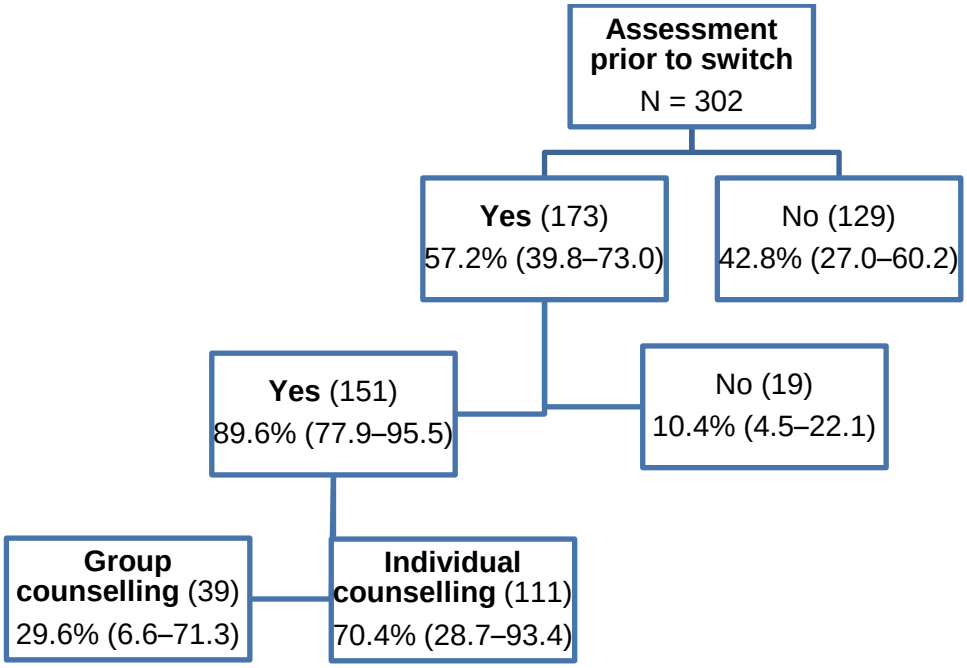


Figure 2: Adherence cascade

Compliance with STGs and Reasons for Switching

Compliance with STGs

This section presents the findings relating to the first objective of the study: "to assess adherence to guidelines for switching ART patients to second-line regimen." In the presentation of the results, the term *compliance* with the guidelines is preferred to *adherence* to the guidelines. The term *adherence* will be reserved for adherence to treatment from the patient perspective.

The overall compliance with the STGs for switching patients to second-line ART was 49.4 per cent (n = 151; CI: 31.9–67.1) (table 25).

Table 25. Compliance Status with STGs

Category (N = 303)	N	%	95% CI
Compliant with STGs	151	49.4	31.9–67.1
Not compliant with STGs	152	50.6	32.9–68.1

As per the guidelines, the following elements were assessed: latest VL prior to switch greater than 1,000, second-latest VL prior to switch greater than 1,000, and record of adherence assessment with the following result.

The record of adherence assessment was missing in 47.4 per cent (n = 103; CI: 38.8–56.2) of the non-compliant records, followed by the absence of second-latest VL (32.1 per cent, n = 77; CI: 19.1–48.6). In some files, more than one element was missing. For instance, 6.6 per cent (n = 10; CI: 0.8–38.3) of the medical records had the two latest VLs lower than 1,000 (A and B), which meant there was no virological failure to support a switch to second-line ART (table 26).

Table 26. Possible Reasons for Non-compliance with STGs

Category (N = 229)	N	%	95% CI
Latest VL prior to switch NOT > 1,000 (A)	1	0.4	0.0–4.7
Second-latest VL prior to switch NOT > 1,000 (B)	6	2.4	0.7–7.9
Second-Latest VL prior to switch absent (C)	77	32.1	19.1–48.6
Adherence assessment = No (D)	103	47.4	38.8–56.2
A and B	10	6.6	0.8–38.3
A and C	10	3.2	1.8–5.7
A and D	5	1.0	0.3–3.4
Other combinations of A, B, C, and D	17	6.9	2.3–18.9

Note: Multiple reasons possible

Compliance with STGs by Type of Facility

Although there was no significant association between the compliance status and the type of facility (p-value = 0.6439; table 27), it is worth noting that CHCs had the highest percentage of compliance with 60.9 per cent (n = 31). The percentage of compliance for hospitals and PHCs was lower than the provincial one with 46.4 per cent (n = 94) and 41.1 per cent (n = 22), respectively.

Table 27. Compliance and Non-compliance with STGs by Type of Facility

	Hospital (N = 194)		CHC (N = 49)		PHC (N = 56)	
Compliance status with STGs	**Freq**	**%**	**Freq**	**%**	**Freq**	**%**
Compliant	94	46.4	31	60.9	22	41.1
Not compliant	100	53.6	18	39.1	34	58.9

Test statistics: Chi-square = 5.5; P-value = 0.6439.

Compliance with STGs by District

Similarly, there was great variation in compliance across the districts. Tshwane district was ranked at the top with 89.6 per cent (n = 40) while Ekurhuleni district was last with only 17.3 per cent (n = 11) of the switches done in compliance with the guidelines. West Rand and Johannesburg had percentages of compliance above the provincial average with 54.9 per cent (n = 27) and 51.7 per cent (n = 67), respectively. Sedibeng was lower with 44.4 per cent (n = 6). It is important to note that the association between compliance with STGs and district was significant with p-value = 0.0258 (table 28).

Table 28. Compliance and Non-compliance with STGs by District

Compliance status with STGs	Johannesburg (N = 141)		Ekurhuleni (N = 59)		Sedibeng (N = 9)		Tshwane (N = 49)		West Rand (N = 45)	
	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
Compliant	67	51.7	11	17.3	6	44.4	40	89.6	27	54.9
Not compliant	74	48.3	48	82.7	3	55.6	9	10.4	18	45.1

Test statistics: Chi-square = 68.6; P-value = 0.0258.

Reasons for Switching Patient to Second-Line ART

The following section addresses the findings related to the second objective of the study: "to document the reasons for switching from first- to second-line regimens."

On the medical record, the prescribers recorded the reason for switching patients from first to second line. According to the guidelines, patients should be switched if there was regimen failure supported by the relevant evidence. However, the reasons given in the medical records for switching patients were the following—

- Regimen failure
- ADRs
- Pregnancy
- Poor adherence
- Initiation on second line
- Not available

Association between Reported Reasons for Switching and Other Factors

Reasons for Switching and Prescriber Qualification

The ranking among the reasons for switching was similar whether a medical doctor had prescribed the switch or a professional nurse (table 29). *Regimen failure* came first (Doctor: 57.7 per cent, n = 151; Professional nurse: 54 per cent, n = 12), followed by the *absence of recorded reason (not available)* for switching (Doctor: 13.6 per cent, n = 33; Professoinal nurse: 22.5 per cent, n = 8). *ADR* was third (Doctor: 13.4 per cent, n = 42; Professional nurse: 12.8 per cent, n = 2), and *pregnancy* fourth (Doctor: 8.4 per cent, n = 25; Professional nurse: 9.6 per cent, n = 3). Only medical doctors (2.6 per cent, n = 14) had initiated patients on second-line regimens; none of the professional nurses did (0.0 per cent, n = 0). With a p-value of 0.6524, the association between the qualification of the prescriber and the reasons for switching was not significant.

Table 29. Qualification of Prescriber and Reason for Switching

	Qualification of prescriber			
	Doctor (N = 277)		Professional nurse (N = 26)	
Reason for switch	**Frequency**	**%**	**Frequency**	**%**
ADR	42	13.4	2	12.8
Initiated on second line	14	2.6	0	0.0
Not available	33	13.6	8	22.5
Poor adherence	12	4.3	1	1.1
Pregnancy	25	8.4	3	9.6
Regimen failure	151	57.7	12	54.0

Test statistic: Chi-square = 3.94; P-value = 0.6524.

Reasons for Switching and Gender

Reasons for switching were significantly (p-value = 0.0196, table 30) associated with gender. Whereas 70.4 per cent (n = 62) of men were switched because of *regimen failure*, only 51 per cent (n = 109) of the women were switched for that reason. *Adverse drug reaction* came second for males (16.5 per cent, n = 17) and third for females (12.7 per cent, n = 30). More females (16.8 per cent, n = 34) had no recorded reasons for switching compared to males (9.1 per cent, n = 9). Interestingly, 1.8 per cent (n = 3) of the males and 2.9 per cent (n = 12) of the females were initiated directly on second-line ART.

Table 30. Gender and Reason for Switch

Reason for switch	**Male (N = 94)**		**Female (N= 224)**	
	Frequency	**%**	**Frequency**	**%**
ADR	17	16.5	30	12.7
Initiated on second line	3	1.8	12	2.9
NA	9	9.1	34	16.8
Poor adherence	3	2.2	10	4.4
Pregnancy	-	-	29	12.2
Regimen failure	62	70.4	109	51.0

Test statistic: Chi-square = 21.18; P-value = 0.0196.

Reasons for Switching and Pregnancy

Pregnancy was the stated reason for switching for 12.2 per cent (n = 29) of women. Table 31 illustrates the significant association (p-value=0.0274) between pregnancy and the recorded reason for switching. Only 14 of the women having *pregnancy* as reason for switching had their pregnancy recorded in their medical file. Twelve women were switched for *pregnancy* with no record of it in their files. Still *pregnancy* became the second reason for switching in pregnant women (34.1 per cent, n=14) compared to a low 5 per cent (n=12) in non-pregnant females. R*egimen failure* stayed the first reason for pregnant (43.8 per cent, n=12) and non-pregnant (53.1 per cent, n=82) women.

Table 31. Pregnancy and Reason for Switch

	Pregnant (N = 37)		Not pregnant (N = 161)	
Reason for switch	**Frequency**	**%**	**Frequency**	**%**
ADR	1	9.3	26	13.9
Initiated on second-line	6	5.1	5	2.6
NA	3	6.7	28	20.4
Poor adherence	1	1.0	8	5.0
Pregnancy	14	34.1	12	5.0
Regimen failure	12	43.8	82	53.1

Test statistic: Chi-square = 32.3; P-value = 0.0274.

Reasons for Switching among Medical Records Compliant with STGs

The medical records of the patients switched in compliance with the guidelines showed two consecutive viral loads greater than 1,000 copies per millilitre, thus providing the necessary supporting evidence for *regimen failure* as the reason for switching.

Surprisingly, of 151 patients switched in compliance with the guidelines, *regimen failure* was the stated reason for switching in only 85. Although the supporting laboratory information was available, prescribers justified the switch with reasons other than *regimen failure*.

Reasons for Switching by District

Regimen failure was the sole (100.0 per cent, n = 6) recorded reason for switching among patients attending facilities in Sedibeng district. *Regimen failure* was the most common reason for switching in all the districts except Ekurhuleni, which had the lowest percentage of patients switched for *regimen failure* (21.2 per cent, n = 2). In that district the majority (76.2 per cent, n = 8) of patients had no recorded reason for switching. West Rand, with 39.8 per cent (n = 8), showed a relatively high percentage of the switches caused by *ADRs*. The association between district and reason for switching was not significant (p-value = 0.0772; table 32).

Table 32. Reason for Switch among Compliant by District

	District									
Reason for switch among compliant	**Johannesburg (N = 67)**		**Ekurhuleni (N = 11)**		**Sedibeng (N = 6)**		**Tshwane (N = 40)**		**West Rand (N = 27)**	
	Freq	**%**	**Freq**	**%**	**Freq**	**%**	**Freq**	**%**	**Freq**	**%**
ADR	10	16.1	0	0.0	0	0.0	2	6.7	8	39.8
Initiated on second line	2	1.1	1	2.6	0	0.0	1	1.8	0	0.0
Not available	7	11.8	8	76.2	0	0.0	6	17.1	2	5.1
Poor adherence	3	1.7	0	0.0	0	0.0	4	11.0	0	0.0
Pregnancy	8	9.2	0	0.0	0	0.0	2	6.4	2	5.1
Regimen failure	37	60.1	2	21.2	6	100.0	25	57.0	15	50.1

Test statistic: Chi-square = 66.92; P-value = 0.0772.

Reasons for Switching by Type of Facility

Although *regimen failure* was the first reason across the three types of facility, the percentages varied from 46.9 per cent (n = 11) for PHCs to 51.1 per cent (n = 52) for hospitals and 61.0 per cent (n = 18) for CHCs. The absence of stated reason came second for the hospitals (20.8 per cent, n = 14) and CHCs while *ADR* was second for PHCs with a high 33.2 per cent (n = 5). The association with the type of facility was not significant (p-value = 0.5751; table 33).

Table 33. Reasons for Switching among Compliant by Facility Type

	Hospital (N = 94)		CHC (N = 31)		PHC (N = 22)	
Reason for switch	**Freq**	**%**	**Freq**	**%**	**Freq**	**%**
ADR	12	13.9	3	9.0	5	33.2
Initiated on second line	2	0.7	1	2.4	1	1.3
Not available	14	20.8	8	23.5	1	6.0
Poor adherence	7	7.9	0	0.0	0	0.0
Pregnancy	7	5.5	1	4.0	4	12.6
Regimen failure	52	51.1	18	61.0	11	46.9

Test statistic: Chi-square = 18.49; P-value = 0.5752.

Adverse Drug Reaction as a Reason for Switching

Among the patients having *ADR* as the recorded reason for switching, the majority (23.0 per cent, n = 23, table 34) were initiated on the D4T + 3TC + EFV regimen. Data on the nature of the ADRs were not collected. The high prevalence of ADRs in this group could be explained by the fact that the majority of patients had been initiated on this regimen (41.8 per cent, n = 158; table 19).

Table 34. ART Regimen at Initiation and ADR as Reason for Switch

ART regimen at initiation	**Frequency**	**%**
AZT+3TC+NVP	1	6.7
AZT+3TC+EFV	0	0
D4T+3TC+NVP	2	1.8
D4T+3TC+EFV	23	23.0
TDF+3TC+NVP	2	4.8
TDF+3TC+EFV	1	3.9
Other regimen	5	5.0

Regimen Failure as the Reason for Switching

The results mentioned in the previous sections raised concerns about the link between compliance with the guidelines and the stated reasons for switching. Some medical records

showed a reason for switching other than *regimen failure* whereas the laboratory data proved an actual regimen failure.

This section presents findings related to the situation of patients switched for *regimen failure* where the switch was not done in compliance with the guidelines. This was the case for 53.3 per cent (n = 82; table 35) of the patients. It was important to determine which one of the necessary elements for compliance was missing. Of the 82 non-compliant medical records with *regimen failure,* 16 had the first VL either absent or lower than 1,000 copies and a further 41 had the second VL absent or lower than 1,000 copies.

Table 35. Compliance and Non-compliance with STGs among *Regimen Failure* Group

Compliance status (N = 167)	Frequency	%	95% CI
Compliant	85	46.7	27.0–67.5
Non-compliant	82	53.3	32.5–73.0

A total of 57 patients had *regimen failure* recorded on their files as the reason for switching in the absence of supporting laboratory evidence.

Regimen Failure as Reason for Switching by Type of Facility

Among the patients switched for *regimen failure*, both PHCs (59.8 per cent, n = 13) and hospitals (58.8 per cent, n = 55) had a higher percentage of not compliant compared to compliant. The CHCs showed an opposite trend with 45.6 per cent (n = 14) of the patients not switched in compliance with the guidelines. There was no significant association between compliance status among the *regimen failure* group and the type of facility (p-value = 0.7027; table 36).

Table 36. Compliance and Non-compliance with STGs by Facility among *Regimen Failure* Group

Compliance status with STGs	Hospital (N = 107)		CHC (N = 32)		PHC (N = 24)	
	Freq	%	Freq	%	Freq	%
Compliant	52	41.2	18	54.4	11	40.2
Not compliant	55	58.8	14	45.6	13	59.8

Test statistics: Chi-square = 2.2; P-value = 0.7027.

Regimen Failure as Reason for Switching by District

The association between regimen failure as a reason for switching with the districts was significant (p-value = 0.0459; table 37). At district level, the trends of non-compliance with the guidelines among the *regimen failure* group were similar to the ones found in the overall population. Ekurhuleni had the highest percentage of non-compliance with 93.8 per cent (n = 30) and Tshwane the lowest with 15.7 per cent (n = 8). Sedibeng and West Rand showed percentages of non-compliance of 55.6 per cent (n = 3) and 54.0 per cent (n = 8),

respectively. In Johannesburg district, 37.8 per cent (n = 33) of the patients switched for *regimen failure* had not been switched in compliance with the guidelines.

Table 37. Compliance and Non-compliance with STGs by District among *Regimen Failure* Group

Compliance status with STGs	Johannesburg (N = 70)		Ekurhuleni (N = 32)		Sedibeng (N = 9)		Tshwane (N = 33)		West Rand (N = 23)	
	Freq	%	Freq	%	Freq	%	Freq	%	Freq	%
Compliant	37	62.2	2	6.2	6	44.4	25	84.3	15	46.0
Not compliant	33	37.8	30	93.8	3	55.6	8	15.7	8	54.0

Test statistics: Chi-square = 51.0; P-value = 0.0459.

Other Factors Contributing to the Switch

In accordance with the third objective of the study, "to identify clinical and other factors contributing to the switch to second line", further associations were explored to identify the factors having a potential influence on the switch to second-line ART.

Association between CD4 Count and Duration on First-Line ART

A regression analysis was performed to establish the relation between the CD4 count at ART initiation and the number of months on first line—

- Y = number of months on first-line ART, and X = CD4 count at initiation.
- Fitted equation: $Y = 22.29 + 0.05X$.
- Standard errors: For intercept = 1.968 and for the slope = 0.010.
- The fitted equation was significant F (1,179) = 24.35 and p-value = 0.000.

The equation can be used to predict the number of months on first line given CD4 count at initiation. For instance, if X increased by one unit, Y increased by 0.05. Note that the fitted regression equation was based on the study sample, patients already on second-line ART.

The scatter plot (figure 3) showed that the majority of the patients had been initiated at CD4 count lower than 200 CD4 per microlitre. This finding was coherent with the CD4 threshold used prior to 2012.

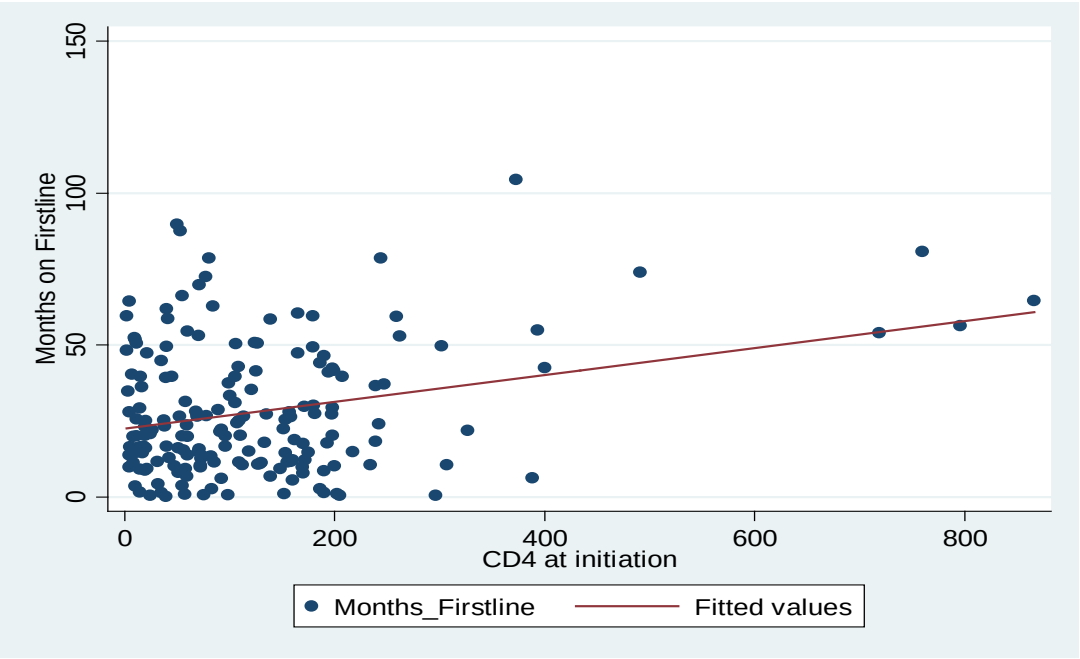


Figure 3: Scatter plot relating number of months on first line to CD4 at initiation

Relating ART Regimen at Initiation to Number of Months on First-Line ART

Knowing the relationship between the regimen at initiation and the number of months the patient stayed on first-line ART is useful in planning for programmes. For this purpose, an analysis of variance was fitted using the number of months on first line as a dependent variable to test if the ART regimen at initiation was significantly different. Only the significant difference (F-value = 8.76; numerator degrees of freedom = 6 and denominator degrees of freedom = 246; mean square error (MSE) = 447.5 and P-value = 0.000) were presented.

Patients initiated on TDF/3TC/EFV-containing regimens stayed significantly shorter on first line compared to patients initiated on AZT/3TC/EFV (−26 months, p-value = 0.004), on AZT/3TC/NVP (−27.58 months, p-value = 0.049), on D4T/3TC/EFV (−24.3 months, p-value = 0.000), or on other regimens (−37.44 months, p-value = 0.000) (table 38).

Similarly, TDF/3TC/NVP-initiated patients stayed 25.134 months less on first-line (p-value = 0.025) than D4T/3TC/EFV-initiated patients and 38.27 months less (p-value = 0.002) than patients initiated on other regimens. As TDF/3TC/EFV regimen was the first choice for first-line ART in the 2010 South African guidelines, this raised concerns about early switch to second line for a majority of patients.

Table 38. Summary of Months on First-Line ART for ART Regimen at Initiation

ART regimen code	ART regimen at initiation	Frequency	Mean	Standard deviation	Significant pairwise comparison	P-value
(1)	AZT+3TC+NVP	7	37.5	20.6	(1) vs. (6)	0.049
(2)	AZT+3TC+EFV	14	36.3	23.4	(2) vs. (6)	0.004
(3)	D4T+3TC+NVP	35	23.1	17.8	(4) vs. (6)	0.025
(4)	D4T+3TC+EFV	149	34.2	21.5	(4) vs. (5)	0.000
(5)	TDF+3TC+NVP	8	9.0	5.9	(4) vs. (7)	0.011
(6)	TDF+3TC+EFV	27	9.9	6.6	(5) vs. (7)	0.002
(7)	Other regimen	13	47.3	40.4	(6) vs. (7)	0.000

Determinants of Compliance with STGs

Identifying potential determinants of compliance was important to get a deeper understanding of the factors influencing the compliance with STGs. Understanding the factors influencing compliance with guidelines would assist in designing appropriate interventions where and when needed.

Factors associated with compliance status were highlighted in previous sections. Logistic regression analysis was performed to identify the significant determinant of compliance. A multivariate logistic regression was fitted using determinants identified to be significant by bivariate logistic regression analysis. Note that an *odds ratio (OR) = 1* is the null value for logistic regression and represents no difference between the two variables being tested.

Gender (p-value = 0.931), age group (p-value = 0.128), pregnancy (p-value = 0.374), and the number of months on first-line ART (p-value = 0.074) were not significant determinants of compliance with STGs (table 39). The type of facility was not a significant determinant either; p-values for CHC and PHC are 0.066 and 0.227, respectively.

In contrast, the district the patient attends was a significant determinant of compliance with guidelines. For instance, patients from Ekurhuleni district were significantly (OR = 0.20; P-value = 0.000) less likely to comply with guidelines relative to patients from Johannesburg. In contrast, patients from Tshwane were significantly (P-value = 0.000) 8.05 times more likely to be switched in compliance with the guidelines than patients from Johannesburg. Although the effect decreased (OR = 5.88 for Tshwane and OR = 0.19 for Ekurhuleni), the significance of the relation still held in the multivariate analysis (p-value = 0.000 for both). Attending facilities in Sedibeng or West Rand district were not significantly related to change in compliance status compared to Johannesburg.

Table 39. Logistic Regression (Bivariate) on Compliance Status with STGs

		Bivariate			Multivariate (N = 281; *R*-squared = 0.27)		
Category	**Category levels**	**OR**	**95% CI**	**P-values**	**OR**	**95% CI**	**P-values**
Gender	Male vs. Female	1.02	0.63–1.67	0.931			
Age	15 to 34 vs. 35+ years	0.61	0.32–1.15	0.128			
	Johannesburg	1			1		
	Ekurhuleni	0.20	0.09–0.44	0.000	0.19	0.08–0.43	0.000
	Sedibeng	0.74	0.17–3.34	0.700	0.60	0.10–3.60	0.576
	Tshwane	8.05	3.33–19.50	0.000	5.88	2.22–15.60	0.000
District	West Rand	1.14	0.44–2.90	0.791	1.52	0.59–3.91	0.384
	Hospital	1					
Type of Facility	CHC	1.83	0.96–3.49	0.066			
	PHC	0.69	0.38–1.26	0.227			
Pregnancy	Pregnant (No vs. Yes)	0.71	0.33–1.51	0.374			
Months on first line	Months on first line	0.99	0.97–1.00	0.074			

Expenditure Analysis

According to the fourth objective of the study, "to calculate the cost implications of lack of compliance with ART guidelines," further analyses (table 40) were performed to calculate the financial implications of poor compliance with guidelines in switching patients to second-line ART.

At the time of the study, the average cost of treatment for one adult patient was R 4,670 per year for second-line ART and R 1,442 per year for first-line ART. Based on consumption data from the MSD, there were an estimated 19,000 patients on second-line ART attending public healthcare facilities in Gauteng Province in 2011. This translates to an estimated cost of R 88.7 million for the year 2011 for the province. The results presented in the previous section show that only 49.4 per cent of the patients had been switched according to the guidelines. The remaining 50.6 per cent have then been wrongfully switched and should still be on first-line ART.

In the event of 100 per cent compliance with the guidelines, only 49.4 per cent (9,386) of patients would have been switched to second line while the remaining 50.6 per cent (9,614) would have been kept on first line. The estimated annual cost for this scenario was R 57.69 million.

Improving the level of compliance with the STGs to 100 per cent was associated with an estimated saving of R 31 million for the year 2011.

Table 40. Comparison of Cost of Treatment between Current Situation and Theoretical Situation with 100 per cent Compliance with STGs

		Actual situation: 49.4% of switches done in compliance with STGs	**Theoretical situation: 100% of switches done in compliance with STGs**
Percentage of patients	Kept on first line	0	50.60
	Switched to second line	100	49.40
Number of patients	First line	0	9,614
	second line	19,000	9,386
Average annual cost (R)	First line: 1,442/year/patient	0	13,863,388
	Second line: 4,670/year/patient	88,730,000	43,832,620
Total		88,730,000	57,696,008

DISCUSSION

Assessing Compliance with Guidelines for Switching ART Patients to Second-Line Regimen

The results highlighted the low percentage (49.4 per cent; CI: 31.9–67.1) of compliance with the STGs for switching patients to second-line ART. This finding is partly explained by a lack of systematic adherence assessment in 47.4 per cent of the non-compliant medical records. Only 57.2 per cent of the patients switched to second line had been assessed for adherence prior to the switch. Of the 173 patients assessed, only 151 received adherence counselling. The role played by adherence to treatment in virological failure does not seem to have received the necessary attention from the prescribers. However, Orrell et al.[15] reported how targeted adherence interventions were implemented within the cohort of patients as an effective means to overcome the initial virological breakthrough. The 2010 South African guidelines[4] (p. 20) reinforced the importance of adherence counselling with the statement:

> "Virological failure is almost always due to poor adherence, often due to poor attention by the clinician to drug toxicity, or where social factors have not been addressed. Rapid attention to drug toxicity or social factors, with better adherence, may allow resuppression of the virus in many cases."

Very worrying was the role played by the absence of the second VL (32.1 per cent) in the non-compliance to the guidelines as it means that prescribers switched patients without confirmation of virological failure. This raised the question of premature or unnecessary switching to second line and of the utilisation of lab information to support clinical decisions.

The regression analysis showed that the only significant determinant of compliance with the guidelines was the district attended by the patients. Facilities located in Sedibeng, West Rand, and Johannesburg district had similar results in terms of compliance. Compared to Johannesburg, patients attending facilities in Tshwane were significantly more likely to be switched to second-line ART in compliance with the guidelines; in contrast, the odds to be switched according to the guidelines were significantly lower in Ekurhuleni facilities than in Johannesburg's. Because the type of facility had no significant influence, one can infer that the preceding findings apply to hospitals, CHCs, and PHCs in the districts.

Documenting the Reasons for Switching from First- and Second-Line Regimens

This study found that 147 patients were switched for reasons other than regimen failure. Among these reasons were pregnancy, ADRs, poor adherence, or no reason at all, thereby highlighting the deviation from the South African STGs that recommend switching patients in case of proven regimen failure. Interestingly, already in 2004, the South African National Antiretroviral Treatment Guidelines (1st edition. p. 20)[16] stated that "patients who have experienced virological failure with good adherence may be changed to second-line therapy". Both WHO and South African guidelines were revised and updated over the years, but a constant remained through the various editions: the only reason for switching patients to second line is regimen failure.

Adverse drug reaction was the reason for switching for 47 patients and was more frequent for patients initiated on D4T/3TC/EFV. With D4T being slowly phased out from the South African ART programme, one can assume that this number may decrease.

According to the STGs, a switch is considered compliant in the presence of two consecutive VLs greater than 1,000 copies per millilitre, hence providing evidence of regimen failure. However, reasons other than regimen failure were recorded for patients switched in compliance with the guidelines. Despite evidence of regimen failure, the prescriber chose to switch the patient for another reason.

Another very worrying finding was that the recorded reasons for switching were not always supported by laboratory evidence. Within the population switched for regimen failure, only 46.7 per cent was switched in compliance with the guidelines. Among the 82 patients non-compliant (but switched for regimen failure), 57 were non-compliant because of VLs absent or lower than 1,000 copies per millilitre. Prescribers had switched 57 patients for regimen failure without having laboratory data supporting this stated reason.

In this instance, the district played a significant role with trends similar to the ones found for overall compliance. Ekurhuleni had a very low percentage of compliance among the population switched for regimen failure; the opposite was found in Tshwane facilities.

Identifying Clinical and Other Factors Contributing to the Switch to Second Line

The previous sections reported that the district attended by the patients contributed significantly to the level of compliance with the guidelines for switching to second line. There is an opportunity to identify and document the best practices from the district with high levels of compliance and implement them in places showing lower levels of compliance.

The poor record of co-morbidity and co-medication in the patients' ART files was noted across the five districts, highlighting the lack of integration of the ART clinic within the rest of the healthcare facility. It was not possible to assess the potential role of chronic medicine–ARV interaction in the switch raising concerns on the possible mismanagement of ARV side effects.

Both from a public health and programmatic perspective, a meta-analysis on the average duration on first-line ART is needed as the information presented in the available literature was difficult to extrapolate. Orrell et al.[15] reported that only 3 per cent of the patients had been switched to second line in the 32 months of the study. In contrast, Keiser et al.[10] highlighted a medium time to switching of 15.2 months in sites from Sub-Saharan Africa with VL monitoring. In this study, the boxplot on the number of months on first line showed that patients had stayed a mean of 30.13 months on first line before being switched. Further, 75 per cent of patients had been on first line for less than four years before being switched; among them, 25 per cent stayed for just over a year. The relation established between the CD4 count and number of months through the fitted equation supported this finding with an estimated duration on first line of 27.29 months and 32.29 months for a CD4 count at initiation of 100 CD4/millilitre and 200 CD4/millilitre respectively. The relation between the CD4 count and the number of months on first line should be noted but used with caution

because the study sample was already on first line. However, it should be kept in mind as the programme is ageing and patients initiated prior to 2012 had CD4 lower than 200.

The finding that patients initiated on tenofovir-containing regimen stayed a shorter time on first-line regimen was of concern as it is the preferred regimen for first-line ART. With D4T being slowly phased out in the South African ART programme, the choice of first-line ART regimen will decrease from six to four—hence the importance of compliance with the standardised monitoring of ART patients to detect and prevent toxicity.

Cost Implications of Lack of Adherence to ART Guidelines

In mid-2011, a total of 1.79 million (95% CI 1.65 million to1.93 million) patients were receiving ART in South Africa. The majority of patients (85 per cent) were treated in the public sector. L. F. Johnson[17] reported that Gauteng is the province with the second largest number of patients (439,000 in 2011). The success of the HIV Counselling and Testing campaign led to a sharp increase in the number of patients initiated on ART. Although the average annual cost of treatment has decreased significantly for second-line regimens (R 2,857.08), thanks to the new contract for ARVs,[18] it is still more than twice the cost of first line (R 1,118.75). In this context, strengthening compliance with the guidelines is crucial, as the financial consequences of poor compliance are heavy. Based on the current contract prices, 50.6 per cent non-compliance with the guidelines cost an extra R 8.79 million per year per 10,000 patients on second-line ART. As the programme ages and the number of patients put on treatment increases dramatically, the number of patients experiencing regimen failure will keep growing. It is essential to ensure that only patients with confirmed virological failure and good record of adherence are switched to second line.

CONCLUSION AND RECOMMENDATIONS

The low levels of compliance with the 2010 South African *Clinical Guidelines for the Management of HIV and AIDS in Adults and Adolescents* have implications for the long-term implementation of the ART programme in terms of cost and planning with scale-up of financial consequences from provincial to national levels. With few options available to patients on second-line ART in case of regimen failure, implications in terms of public health should also be considered.

However, the disparity between districts can be used to document best practices on the one hand and strengthen systems in the poorer performing districts on the other.

Recommendations based on the findings are presented below.

Recommendations

Promote Adherence Assessment and Counselling

The 2010 guidelines did not explicitly specify what "a good record of adherence" was or when the adherence assessment and counselling should take place and what it should entail.

Provincial guidelines for implementation of adherence assessment and counselling would assist in harmonising the situation. It is thus recommended to develop such guidelines to address and clarify the definition of "a good record of adherence", standardize the adherence assessment (tool use, timing with regard to fist VL>1,000 copies/millilitre, report, and record needed) and harmonise the message provided during counselling.

Reinforce Compliance with STGs

The South African National Department of Health will soon publish new STGs for ART. This can be an opportunity to promote compliance with the guidelines through workshops, posters, and mentoring. Besides the treatment guidelines themselves, emphasis should be put on treatment monitoring and pharmacovigilance. The impact of non-compliance on the whole programme and to a larger extent on the health system in the province has to be highlighted as well as every healthcare professional's responsibility to work in compliance with the guidelines.

Strengthen Integration of ART Clinic within Main Clinic

ARVs are potent medicines and as such have side effects and potential to interact with other medicines. Within a parallel system, there are separate files for ARVs and other conditions. This forces prescribers to rely solely on the patient to supply them with information on co-morbidity and/or co-medication. Unfortunately, patients are not always in a position to provide the correct information related to their conditions or treatment. For instance, a patient presenting at the main clinic with psychological side effects of efavirenz could be mistaken for having a mental health disease if he does not inform the prescriber about his ARV treatment. The same would apply for a psychotic patient not informing the prescriber at the

ARV clinic about his condition with the risk of being prescribed efavirenz that will worsen his primary mental health condition.

The process of integrating the ARV pharmacy within the main pharmacy has already started in some facilities in the province; when possible, the integration should be strengthened to accelerate the process for the benefit of the patients.

Collect and Monitor Usage Data to Promote Rational Medicine Use

Up-to-date procurement data from MSD were used as an approximation for ARV usage. The analysis of the quantities issued to the facilities was seen as a signal that triggered further investigation. Over the financial year 2011/12, the ARVs were responsible for the highest pharmaceutical expenditure in the province (quantities of ARVs issued from MSD). With the ART programme growing at an increasing speed, the rational use of ARVs is becoming more and more essential to avoid not only waste of resources but also unnecessary toxicity or resistance. In these circumstances, an integrated and comprehensive system to effectively monitor the prescribing and dispensing of ARVs would be of utmost benefit to ensure rational use of healthcare resources in the province.

APPENDIX A: LIST OF THE HEALTHCARE FACILITIES RANDOMLY SELECTED

#	Names of the facilities randomly selected in low group	#	Names of the facilities randomly selected in medium group	#	Names of the facilities randomly selected in high group
1	Carletonville Hospital	3	Cullinan Rehabilitasie Sentrum	3	Dr. George Mukhari Hospital
2	Chiawelo Clinic	4	Dr Yusuf Dadoo Hospital	4	Edenvale Hospital
4	Dawn Park Clinic	5	Eric Ndeleni Clinic	5	Helen Joseph Hospital
5	Diepsloot Clinic	6	Germiston Hospital	6	Hillbrow Hospital CHC
8	Empilisweni Clinic	8	Jabulani Dumane CHC	8	Muldersdrift Clinic
12	K.T. Motubatse Chc	9	Kagiso Clinic (Thusong)	10	St. Johns Eye Hospital
13	Katlehong North Clinic	11	Kopanong Hospital	11	Tambo Memorial Hospital
15	Kwa-Thema CHC	12	Leratong Hospital		
16	Laudium CHC	15	Mohlakeng Clinic		
17	Lenasia South CHC	19	Tshwane District Hospital		
19	Meyerton CHC				
22	Pholosong Hospital				
23	Pretoria West Hospital				
24	Sebokeng Hospital				
28	Tembisa Main Clinic				
30	Witkoppen CHC				

APPENDIX B: SAMPLE SIZE OF MEDICAL RECORDS PER FACILITY

Low group	Number of files per facility	Medium group	Number of files per facility	High group	Number of files per facility
Carletonville Hospital	6	Cullinan Rehabilitasie Sentrum	4	Dr. George Mukhari Hospital	13
Chiawelo Clinic	2	Dr Yusuf Dadoo Hospital	8	Edenvale Hospital	19
Dawn Park Clinic	2	Eric Ndeleni Clinic-A	2	Helen Joseph Hospital	85
Diepsloot Clinic	4	Germiston Hospital	14	Hillbrow Hospital (CHC)	20
Empilisweni Clinic	0	Jabulani Dumane CHC	7	Muldersdrift Clinic	3
K.T.Motubatse Chc	3	Kagiso Clinic (Thusong)	18	St. Johns Eye Hospital	13
Katlehong North Clinic	4	Kopanong Hospital	7	Tambo Memorial Hospital	15
Kwa-Thema CHC	1	Leratong Hospital	7		
Laudium CHC	5	Mohlakeng Clinic	6		
Lenasia South CHC	2	Tshwane District Hospital	18		
Meyerton CHC	1				
Pholosong Hospital	2				
Pretoria West Hospital	4				
Sebokeng Hospital	2				
Tembisa Main Clinic	7				
Witkoppen CHC	7				

APPENDIX C: DATA COLLECTION SHEET

DATA COLLECTION SHEET					
Date of data collection					
Name of the Institution					
District (tick)	City of Johannesburg	Ekurhuleni	Sedibeng	Tshwane	West Rand
Level (tick)	PHC	CHC	District Hospital	Regional Hospital	Tertiary Hospital
Name of data Collector					

1

Indicator No.	Indicator	Criteria No.	Assessment criteria	Patient medical record n.	Patient medical record n.	Patient medical record n.	Patient medical record n.	Patient medical record n.
1	Patient demographic	1.1	Patient's date of birth (dd/mm/yyyy)					
		1.2	Male (1) / Female (2)					
		1.3	Pregnancy at time of the switch (Y or N)					
2	Current 2nd line regimen (tick)	2.1	TDF + 3TC + LPV/r					
		2.2	AZT + 3TC + LPV/r					
3	Patient's latest CD4 Count	3.1	CD4 Count test result (in cell/mm³)					
		3.2	Date of CD4 Count (dd/mm/yyyy)					
4	Patient's latest Viral Load (VL)	4.1	VL test result (in copies/ml)					
		4.2	Date of VL (dd/mm/yyyy)					
5	ART regimen at initiation	5.1	Date of ART initiation (dd/mm/yyyy)					
		5.2	CD4 Count at time of initiation (in cell/mm³)					
		5.3 (tick)	TDF + 3TC +EFV					
			TDF + 3TC + NVP					
			AZT + 3TC + EFV					
			AZT + 3TC + NVP					
			D4T + 3TC + EFV					
			D4T + 3TC +NVP					
			Paeds 1st line regimen					

2

Indicator No.	Indicator	Criteria No.	Assessment criteria	Patient medical record n.	Patient medical record n.	Patient medical record n.	Patient medical record n.	Patient medical record n.
6	Switch to 2nd line regimen	6.1	**Date switch** to 2nd line (dd/mm/yyyy)					
		6.2	**Date** latest **VL** prior to switch (dd/mm/yyyy)					
		6.3	**Result** latest **VL** prior to switch (in copies/ml)					
		6.4	**Date** 2nd latest **VL** prior to switch (dd/mm/yyyy)					
		6.5	**Result** 2nd latest **VL** prior to switch (in copies/ml)					
		6.6	**Date** latest **CD4 Count** prior to switch (dd/mm/yyyy)					
		6.7	**Result** latest **CD4 Count** prior to switch (cell/mm³)					
		6.8	**Prescriber qualification** (1=MD; 2=PN; 3=SC)					
		6.9	**Stated reason** for switch (as written in medical file)					

3

Indicator No.	Indicator	Criteria No.	Assessment criteria	Patient medical record n.	Patient medical record n.	Patient medical record n.	Patient medical record n.	Patient medical record n.
7	Record of adherence (if Yes, record needs to be present in medical file)	7.1	Record of adherence assessment prior to switch (Y / N)					
		7.2	Record of adherence counselling prior to switch (Y / N)					
		7.3	Type of adherence counselling provided prior to switch 1= group counselling 2= individual counselling					
8	TB co-infection (at the time of switch)	8.1	TB Co-infection Y/ N					
		8.2	Date of TB diagnosis					
		8.3	Date TB treatment initiation					
		8.4	TB treatment category 1 : new case 2 : retreatment 3 : MDR 4 : XDR					

4

Indicator No.	Indicator	Criteria No.	Assessment criteria	Patient medical record n.	Patient medical record n.	Patient medical record n.	Patient medical record n.	Patient medical record n.
9	Other co-morbidities (at the time of the switch)	9.1.1	**Mental health disease Y/N**					
		9.1.2	Diagnosis's date					
		9.1.3	**Prescribed medicines**					
		9.2.1	**Liver failure Y/N**					
		9.2.2	Diagnosis's date					
		9.2.3	**Prescribed medicines**					
		9.3.1	**Renal failure Y/N**					
		9.3.2	Diagnosis's date					
		9.3.3	**Prescribed medicines**					
		9.4.1	**Diabetes Y/N**					
		9.4.2	Diagnosis's date					
		9.4.3	**Prescribed medicines**					
		9.5.1	**High blood pressure Y/N**					
		9.5.2	Diagnosis's date					
		9.5.3	**Prescribed medicines**					

5

APPENDIX D: LETTER TO HOSPITAL CEO

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

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MSH SPS Strengthening Pharmaceutical Systems

Management Sciences for Health
Strengthening Pharmaceutical Systems
Ditsela Place
Corner Duncan and Park street, Hatfield
Pretoria

Enquiries: Dr. Stephanie Berrada
Principal investigator
Tel: 072 786 5627
Fax: 086 559 6408
E-mail: sberrada@msh.org

17 September 2012

To: The Hospital Chief Executive Officer

.....

Dear Colleague,

Re: Study Title: What are the reasons for switching ART patients (adults and adolescents) to 2nd line regimen in public healthcare setting in Gauteng?

The Gauteng Department of Health, in collaboration with Management Sciences for Health's Strengthening Pharmaceutical Systems project (SPS/MSH), is conducting an assessment for the reasons for switching patients on Antiretroviral Treatment (ART) from 1st to 2nd line regimen in public healthcare facilities in Gauteng Province, South Africa.

This evaluation will allow a better understanding of the adherence to standard treatment guidelines (National Department of Health. 2010. Clinical Guidelines for the management of HIV and AIDS in Adults and Adolescents. South Africa) in term of switching patients from 1st line to 2nd line ART regimen and will document the potential reasons for non adherence to standard treatment guidelines.

The results of this assessment will be shared with the Gauteng Department of Health and be used to develop recommendations and identify priority areas for the rational use of 2nd line AntiRetroviral (ARV); more specifically Lopinavir boosted Ritonavir in health care facilities in order to ensure the safe use of medicines by health care workers and patients.

This letter serves to notify you that the study has been approved by the Gauteng Department of Health and that your facility has been selected for the study. The study has also received ethical approval from Pharma-Ethics Independent Research Ethics Committee. The assessment will be conducted as a patient's medical record review using a standardized questionnaire. Full confidentiality will be maintained at all times.

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It will be requested for each facility to assist by providing a list of names or file numbers of all adult patients (more than 15 years old) on second line antiretroviral regimen from their ART register. The designation of the responsible person for the above mentioned task is left at your discretion. The list should be sent to the principal investigator, Dr. Stephanie Berrada.

A predetermined number of files per facility will be randomly selected from the list of patients on second line regimen.

The letter also serves to inform you that the data collection will be performed by a pharmacist or a community service pharmacist nominated by the pharmacy manager from your district.
The clinics and hospitals will receive in due time a letter introducing the data collector (name and ID number) with proposed dates for the data collector to conduct patient record reviews.
The responsible pharmacist in your facility has received a letter informing her/ him about this study.

The list of patients on second line ART is needed at least one week prior to the data collection scheduled to start on the 8th of October. We would really appreciate to receive the list no later than Wednesday the 26st of September.

Your participation will contribute significantly to improving medicine rational utilisation in Gauteng Province.

Mrs. Nocawe Thipa (Chief Director: Clinical Support Services (Co-investigator)), Dr. Zuki Pinini (Director: HIV and AIDS, STIs (Co-investigator)), and Dr. Stephanie Berrada (Principal investigator) would like to thank you for your cooperation and support.

Yours faithfully,

Mrs. Nocawe Thipa

APPENDIX E: LETTER TO HOSPITAL PHARMACY MANAGER

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Management Sciences for Health
Strengthening Pharmaceutical Systems
Ditsela Place
Corner Duncan and Park street, Hatfield
Pretoria

Enquiries: Dr. Stephanie Berrada
Principal investigator
Tel: 072 786 5627
Fax: 086 559 6408
E-mail: sberrada@msh.org

17 September 2012

To: The Hospital Pharmacy manager

.....

Dear Colleague,

Re: Study Title: What are the reasons for switching ART patients (adults and adolescents) to 2nd line regimen in public healthcare setting in Gauteng?

The Gauteng Department of Health, in collaboration with Management Sciences for Health's Strengthening Pharmaceutical Systems project (SPS/MSH), is conducting an assessment for the reasons for switching patients on Antiretroviral Treatment (ART) from 1st to 2nd line regimen in public healthcare facilities in Gauteng Province, South Africa.

This evaluation will allow a better understanding of the adherence to standard treatment guidelines (National Department of Health. 2010. Clinical Guidelines for the management of HIV and AIDS in Adults and Adolescents. South Africa) in term of switching patients from 1st line to 2nd line ART regimen and will document the potential reasons for non adherence to standard treatment guidelines.

The results of this assessment will be shared with the Gauteng Department of Health and be used to develop recommendations and identify priority areas for the rational use of 2nd line AntiRetroviral (ARV); more specifically Lopinavir boosted Ritonavir in health care facilities in order to ensure the safe use of medicines by health care workers and patients.

This letter serves to notify you that the study has been approved by the Gauteng Department of Health and that your hospital has been selected for the study. The study has also received ethical approval from Pharma-Ethics Independent Research Ethics Committee. The assessment will be conducted as a patient's medical record review using a standardized questionnaire. Full confidentiality will be maintained at all times.

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REPUBLIC OF SOUTH AFRICA

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The data collection will be performed by a pharmacist or a community service pharmacist nominated by the pharmacy manager from your district.

The letter also serves to inform you that assistance as been requested from your hospital CEO in providing the following information to the principal investigator, Dr. Stephanie Berrada:

1. List, from the ART register, of the full name (or file number) of the adult patients (more than 15 years old) on second line antiretroviral regimen;

Kindly follow up on this request to ensure that the above information is sent **by Wednesday 26th of September 2012 the latest.**

A predetermined number of files per facility will be randomly selected from the list of patients on second line regimen.
The selected list of patients' name or file number will be shared with the data collectors during the training and planning session scheduled for the 8th of October 2012. Data collection will take place over two week period, from the 8th to the 19th of October 2012.

Your hospital will receive in due time a letter introducing the data collector (name and ID number) with proposed dates for the data collector to conduct patient record reviews. The hospital will be asked to have the selected files ready for review on the chosen date.

Your participation will contribute significantly to improving medicine rational utilization in Gauteng Province.

Mrs. Nocawe Thipa (Chief Director: Clinical Support Services (Co-investigator)), Dr. Zuki Pinini (Director: HIV and AIDS, STIs (Co-investigator)), and Dr. Stephanie Berrada (Principal investigator) would like to thank you for your cooperation and support.

Yours faithfully,

Mrs. Nocawe Thipa

APPENDIX F: LETTER TO DISTRICT CHIEF DIRECTOR

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Management Sciences for Health
Strengthening Pharmaceutical Systems
Ditsela Place
Corner Duncan and Park street, Hatfield
Pretoria

Enquiries: Dr. Stephanie Berrada
Principal investigator
Tel: 072 786 5627
Fax: 086 559 6408
E-mail: sberrada@msh.org

17 September 2012

To: The District Chief Director

.....

Dear Colleague,

Re: Study Title: What are the reasons for switching ART patients (adults and adolescents) to 2nd line regimen in public healthcare setting in Gauteng?

The Gauteng Department of Health, in collaboration with Management Sciences for Health's Strengthening Pharmaceutical Systems project (SPS/MSH), is conducting an assessment for the reasons for switching patients on Antiretroviral Treatment (ART) from 1st to 2nd line regimen in public healthcare facilities in Gauteng Province, South Africa.

This evaluation will allow a better understanding of the adherence to standard treatment guidelines (National Department of Health. 2010. Clinical Guidelines for the management of HIV and AIDS in Adults and Adolescents. South Africa) in term of switching patients from 1st line to 2nd line ART regimen and will document the potential reasons for non adherence to standard treatment guidelines.

The results of this assessment will be shared with the Gauteng Department of Health and be used to develop recommendations and identify priority areas for the rational use of 2nd line AntiRetroviral (ARV); more specifically Lopinavir boosted Ritonavir in health care facilities in order to ensure the safe use of medicines by health care workers and patients.

This letter serves to notify you that the study has been approved by the Gauteng Department of Health and that clinics/ Community Health Centres (CHC)* within your district have been selected for the study. The study has also received ethical approval from Pharma-Ethics Independent Research Ethics Committee. The assessment will be conducted as a patient's medical record review using a standardized questionnaire. Full confidentiality will be maintained at all times.

* list of clinics/ CHCs per district attached

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It will be requested for each facility to assist by providing a list of names or file numbers of all adult patients (more than 15 years old) on second line antiretroviral regimen from their ART register. The designation of the responsible person for the above mentioned task is left at your discretion. The list should be sent to the principal investigator, Dr. Stephanie Berrada.

A predetermined number of files per facility will be randomly selected from the list of patients on second line regimen.

The letter also serves to inform you that the data collection will be performed by a pharmacist or a community service pharmacist nominated by the pharmacy manager from your district.
The clinics and CHCs will receive in due time a letter introducing the data collector (name and ID number) with proposed dates for the data collector to conduct patient record reviews.
The pharmacist manager in your district has received a letter informing her/ him about this study.

The list of patients on second line ART is needed at least one week prior to the data collection scheduled to start on the 8th of October. We would really appreciate to receive the list no later than Wednesday the 26st of October.

The letter also serves to inform you that the data collection will be performed by a pharmacist or a community service pharmacist nominated by the pharmacy manager from your district.

Your participation will contribute significantly to improving medicine rational utilization in Gauteng Province.

Mrs. Nocawe Thipa (Chief Director: Clinical Support Services (Co-investigator)), Dr. Zuki Pinini (Director: HIV and AIDS, STIs (Co-investigator)), and Dr. Stephanie Berrada (Principal investigator) would like to thank you for your cooperation and support.

Yours faithfully,

Mrs. Nocawe Thipa

APPENDIX G: LETTER TO DISTRICT PHARMACY MANAGER

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

Management Sciences for Health
Strengthening Pharmaceutical Systems
Ditsela Place
Corner Duncan and Park street, Hatfield
Pretoria

Enquiries: Dr. S. Berrada
Principal investigator
Tel: 072 786 5627
Fax: 086 559 6408
E-mail: sberrada@msh.org

17 September 2012

To: The Pharmacy manager

.....

Dear Colleague,

Re: Study Title: What are the reasons for switching ART patients (adults and adolescents) to 2nd line regimen in public healthcare setting in Gauteng?

The Gauteng Department of Health, in collaboration with Management Sciences for Health's Strengthening Pharmaceutical Systems project (SPS/MSH), is conducting an assessment for the reasons for switching patients on Antiretroviral Treatment (ART) from 1st to 2nd line regimen in public healthcare facilities in Gauteng Province, South Africa.

This evaluation will allow a better understanding of the adherence to standard treatment guidelines (National Department of Health. 2010. Clinical Guidelines for the management of HIV and AIDS in Adults and Adolescents. South Africa) in term of switching patients from 1st line to 2nd line ART regimen and will document the potential reasons for non adherence to standard treatment guidelines.

The results of this assessment will be shared with the Gauteng Department of Health and be used to develop recommendations and identify priority areas for the rational use of 2nd line AntiRetroviral (ARV); more specifically Lopinavir boosted Ritonavir in health care facilities in order to ensure the safe use of medicines by health care workers and patients.

This letter serves to notify you that the study has been approved by the Gauteng Department of Health and that clinics/ Community Health Centres* (CHCs) within your district have been selected for the study. The study has also received ethical approval from Pharma-Ethics Independent Research Ethics Committee. The assessment will be conducted as a patient's medical record review using a standardized questionnaire. Full confidentiality will be maintained at all times.

*list of clinics and CHCs per district attached

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The letter also serves to inform you that assistance as been requested from your District Chief Director in providing the following information to the principal investigator, Dr. Stephanie Berrada:

- List, from the ART register, of the full name (or file number) of the adult patients (more than 15 years old) on second line antiretroviral regimen;

The letter also serves to request your assistance by providing the following information to the principal investigator, Dr. Stephanie Berrada:

1. For each facility, please indicate whether the patient files are kept at the clinic or with patient.
2. Full name of two pharmacists or community service pharmacists to conduct data collection in selected facilities within City of Tshwane district. The two data collectors should have a valid driving license and a car available; their travel costs will be covered by MSH, as well as a per diem for lunch during data collection.

Kindly ensure that the above information is sent by **Wednesday 26th of September 2012 the latest.**

A predetermined number of files per facility will be randomly selected from the list of patients on second line regimen.
The selected list of patients' name or file number will be shared with the data collectors during the training and planning session scheduled for the 8th of October 2012. Data collection will take place over two week period, from the 8th to the 19th of October 2012.

The clinics and CHCs will receive in due time a letter introducing the data collector (name and ID number) with proposed dates for the data collector to conduct patient record reviews. The clinics and hospitals will be asked to have the selected files ready for review on the chosen date.

Your participation will contribute significantly to improving medicine rational utilization in Gauteng Province.

Mrs. Nocawe Thipa (Chief Director: Clinical Support Services (Co-investigator)), Dr. Zuki Pinini (Director: HIV and AIDS, STIs (Co-investigator)), and Dr. Stephanie Berrada (Principal investigator) would like to thank you for your cooperation and support.

Yours faithfully,

Mrs. Nocawe Thipa

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