Cost Effectiveness Analysis of Two Alternative Interventions for the Integration of Tenofovir into South Africa's Public Sector First Line Antiretroviral Treatment Regimen

By

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DECLARATION

I, Iming Lin, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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Abstract

In 2003, South Africa's National Department of Health (DoH) initiated the roll out of antiretroviral therapy (ART) for HIV positive individuals in the public health sector. Based on World Health Organization (WHO) guidelines, South Africa's ART programme provides a first line regimen based on a backbone of two nucleoside reverse transcriptase enzyme inhibitors (NRTI) with one non-nucleoside reverse transcriptase inhibitor (NNRTI) while the second line regimen is based on a protease inhibitor (PI) with two NRTIs. Similar to many developing countries, South Africa's NRTI backbone in the first line treatment regimen is stavudine (d4T) combined with lamivudine (3TC), and the NNRTI which is either efavirenz (EFV) or nevirapine (NVP). In some cases, stavudine is replaced with the NRTI zidovudine (AZT) in the first line regimen. Both d4T and AZT have been recognized to contribute to drug related toxicities or side effects, particularly lactic acidosis, lypodystrophy, peripheral neuropathy, and anaemia. However, developing country governments have been limited to these NRTI choices due to the higher cost of alternative treatment options.

There is compelling logic that the life long commitment of ART can be made more tolerable, and that adherence among patients and the success of a public sector ART programme can be increased through the provision of ART regimens with the fewest side effects. In addition, the costs and complications associated with treating and managing adverse events associated with d4T and AZT create further burden on the public health sector. By providing tenofovir as an alternative to d4T and AZT in first line ART therapy, the South African government would increase the chance of successful ART therapy for patients and the long-term success of the national ART programme.

This cost effectiveness analysis will compare the currently available first line ART options (the status quo) to two alternative options in order to assess the cost-effectiveness of the provision of tenofovir in place of d4T/AZT.

Table of Contents

List of Abbreviations

DoH- National Department of Health
ART- antiretroviral therapy
WHO- World Health Organization
NRTI- nucleoside reverse transcriptase inhibitor
NNRTI- non-nucleoside reverse transcriptase inhibitor
PI- protease inhibitor
d4T- stavudine
3TC- lamivudine
EFV- efavirenz
NVP- nevirapine
AZT- zidovudine
TDF- tenofovir DF
MCC- Medicines Control Council
ICER- incremental cost effectiveness ratio
IDU- GF Jooste Infectious Diseases Unit
IDR- GF Jooste Infectious Diseases Referral Unit
CHC- community health centre
QALY- quality adjusted life year
NHLS- National Health Laboratory Services
CPIX- Consumer Price Index excluding interest rates on mortgage bonds

List of Tables and diagrams

Chapter 1: Introduction

In 2003, South Africa's National Department of Health (DoH) initiated the roll out of antiretroviral therapy (ART) for HIV positive individuals in the public health sector. Based on World Health Organization (WHO) guidelines, South Africa's ART programme provides a first line regimen based on a backbone of two nucleoside reverse transcriptase enzyme inhibitors (NRTI) with one non-nucleoside reverse transcriptase inhibitor (NNRTI) while the second line regimen is based on a protease inhibitor (PI) with two NRTIs. Similar to many developing countries, South Africa's NRTI backbone in the first line treatment regimen is stavudine (d4T) combined with lamivudine (3TC), and the NNRTI which is either efavirenz (EFV) or nevirapine (NVP). In some cases, stavudine is replaced with the NRTI zidovudine (AZT) in the first line regimen. Both d4T and AZT have been recognized to contribute to drug related toxicities or side effects, particularly lactic acidosis, lypodystrophy, peripheral neuropathy, and anaemia. However, developing country governments have been limited to these NRTI choices due to the higher cost of alternative treatment options.

Patients experiencing severe d4T and AZT adverse events have limited ART options. Depending on the severity of the adverse event, patients may be required to temporarily discontinue ART until the condition normalizes. The monitoring and treating of these adverse events has serious cost implications for the public health sector. When patients resume ART, often their only treatment option is the PI based second line regimen. This, of course, limits future ART treatment options for the patient as, at present, no other treatment regimens are available in South Africa. In addition to the patient experiencing severe adverse events requiring a change of treatment regimen, many of the unpleasant side effects of d4T and AZT may also contribute to non-adherence and defaulting of ART among patients.

In more affluent countries, the first line ART therapy of choice has moved from d4T and AZT based regimens, to a once daily Tenofovir DF (TDF) based regimen. While the cost of tenofovir is significantly higher than d4T and AZT, tenofovir has been shown to have far fewer side effects and to have no association with lactic acidosis, lypodystrophy, peripheral neuropathy, or anaemia. At present, despite being registered with the Medicines Control Council (MCC), tenofovir is

available to only a very limited number of South African public sector patients through a compassionate programme of the manufacturer, Gilead Pharmaceuticals.

There is compelling logic that the life long commitment of ART can be made more tolerable, and that adherence among patients and the success of a public sector ART programme can be increased through the provision of ART regimens with the fewest side effects. In addition, the costs and complications associated with treating and managing adverse events associated with d4T and AZT create further burden on the public health sector. By providing tenofovir as an alternative to d4T and AZT in first line ART therapy, the South African government would increase the chance of successful ART therapy for patients and the long-term success of the national ART programme.

This study will compare the currently available first line ART options (the status quo) to two alternative options in order to assess the cost-effectiveness of the provision of tenofovir in place of d4T/AZT. Option one is the provision of tenofovir for patients after the development of side effects. Option two is the substitution of d4T/AZT for tenofovir in all patients with predisposing factors for the development of specified side effects.

Chapter 2: Literature Review

As this study deals with clinical management of patients on ART, this literature review will cover both clinical aspects of ART as well as technical aspects of cost-effectiveness studies. The first three sections provide background on d4t, AZT, and TDF toxicity. Sections 4 through 6 provide information on comparisons between d4T and TDF, AZT and TDF, and TDF only. The final section provides information on cost-effectiveness studies including health economics, economic evaluation, and cost-effectiveness analysis.

1. D4T Toxicity

Despite its effectiveness and affordability, d4T is no longer used in most affluent countries because of the numerous associated side effects. The most prevalent of these side effects are peripheral neuropathy, hyperlactataemia and lactic acidosis, lipodystrophy, hepatoxicity, pancreatitis, and hepatosteatosis.

In a study conducted in Khayelitsha, South Africa, 20.8% of patients started on d4T based ART were switched off d4T by year 3. Categorised by adverse event, 4.7% of patients switched due to symptomatic hyperlactataemia, 9,0% due to lipodystrophy, and 6,2% due to peripheral neuropathy (Boulle, et al., 2007). The association of d4T with hyperlactataemia and lactic acidosis is particularly important due to the high mortality rate of 30-60% associated with these effects(Aid for Aids, 2007). Even in cases of less severe lactic acidosis, patients are permanently restricted from taking d4T.

In another study, 63% of patients on a d4T based regimen had signs of lipodystrophy by 14 months of treatment (McComsey, et al., 2004). Lipodystrophic changes include the loss of fat from face and limbs with an increase of fat on the torso. ART side effects that lead to physical disfigurement (lipodystrophy), physical discomfort (peripheral neuropathy), and severe toxicities (hyperlactataemia and lactic acidosis) may discourage patients from taking their ART.

Table A below details the major side effects of d4T, their symptoms, and predisposing factors. In tenofovir based ART, none of these side effects would be relevant.

Table A: Side effects of d4T

Side Effect	Symptoms	Predisposing Factors
Symptomatic Hyperlactataemia/ Lactic Acidosis	• Nausea • Vomiting • Abdominal pain • Rapid weight loss (5kg in 3 months) • Fatigue (Kimani, et al., 2006) • Shortness of breath (Mwebaze, et al., 2006) • Bloating (Lonergan, et al., 2004) • Diarrhoea • Weight gain of ≥ 6kg in first 3 months ART • Weight loss ≥ 3kg in last 3 months prior to diagnosis • Concurrent PNP • 6-14 months on ART treatment (Osler, et al., 2007) • Peripheral oedema • Peripheral neuropathy • Myalgia • Unexplained tachypnoea	• Female gender • Baseline weight >60kg • Weight >75kg • Low CD4 • High WHO stage • Muscle cramps • High BMI (mean 27) (Mohapi, et al., 2006) • Chronic renal failure • Pregnancy (National Department of Health South Africa, 2004) • Older age
Lipodystrophy	• Recent weight loss • Fat loss in arms, legs, buttocks, face • Fat gain in chest	• Female gender • Baseline weight >75kg • >6months ART (Van Griensven, et al., 2006) • Longer HIV • Advanced HIV (low CD4) • More NRTI experience • Older age • Lower pre-therapy fat
Peripheral neuropathy	• Burning • Aching • Tingling	• Greater age • Higher WHO stage (weak associations) • CD4 <200 • Female gender (Dragovic & Jevtovic 2003)

2. AZT Toxicity

The side effect profile of AZT is less severe than d4T, however, a significant number of patients are affected by these side effects, influencing their ART options. Similar to d4T, AZT is associated with pancreatitis and hepatosteatosis. The most common side effects of AZT are anaemia and neutropenia. In the Khayelitsha study mentioned above, 7.8% of individuals switched from AZT by 3 years of treatment due to anaemia or neutropenia[1]. In cases where patients are already restricted from d4T, the only present option in the public sector is a Kaletra (PI) based regimen. As Kaletra is the backbone of South Africa's public sector second line regimen, placing patients on a first line Kaletra regimen effectively eliminates second line treatment options. If patients fail their Kaletra first line option, there is no further ART treatment available to them.

Table B below details the major side effects of AZT, symptoms, and predisposing factors.

Table B: Side effects of AZT

Side Effect	Symptoms	Predisposing Factors
Anaemia	• weakness • fatigue	• Baseline CD4 <50 • older age • higher WHO stage
Neutropenia	• fevers • infections	• Baseline CD4 <50 • older age • higher WHO stage

3. Tenofovir toxicity

With a longer half life than other NRTIs, tenofovir has the convenient benefit of once daily dosing, as opposed to D4T and AZT that require twice daily dosing. Combined with 3TC, tenofovir can be taken once a day, with or without food. The simplicity of dosing and few side effects makes tenofovir a popular ART choice in countries where it is available.

Primary concerns about tenofovir relate to nephrotoxicity[1] and reductions in bone mineral density. Tenofovir's association with decreased bone density brings into question its suitability for use in children and pregnant women. Animal studies with high-level doses (up to 14 times that given to humans) of tenofovir have not shown links to birth defects. Long-term studies on monkeys have indicated the presence of biomarkers for defects in both mothers and foetuses. In contrast to other NRTIs, tenofovir does not cause lactic acidosis, pancreatitis, anaemia, or neuropathy.

The primary side effect of concern for tenofovir is the drug's impact on renal function as analysed through creatinine clearance and creatinine levels. Although clinical trials have shown tenofovir to have an excellent renal safety profile, there have been cases of renal impairment in various cohort studies and trials. In most cases, nephrotoxicity has occurred in patients with baseline abnormal renal function.

An analysis of a prospective study comparing tenofovir (n= 344) with an alternative NRTI (n=314), showed that there were statistically significant increases in creatinine levels and decreases in creatinine clearance (indicating a tendency towards poorer renal function) in tenofovir patients. However, the changes in creatinine and creatinine clearance were not large enough in magnitude to motivate for a change in regimen, indicating an unclear clinical significance (Gallant, et al., 2005). Another study looking at the association between tenofovir and hypophosphatemia[2] (often linked with renal dysfunction), noted that the incidence of hypophosphatemia was slightly elevated in the tenofovir group but was not statistically different from the non-tenofovir group (Buchacz, et al., 2006).

In contrast to these studies indicating the uncertainty of the extent of clinical side effects of tenofovir, other researchers have reported case descriptions of tenofovir associated renal dysfunction (Karras, et al., 2003), and cohort studies showing elevated creatinines or declining creatinine clearances. One study, with mean patient duration on tenofovir of 2.2 years, reports a decline in creatinine clearance in 7% of patients (>30% decline) with predictors for tenofovir related renal dysfunction being concurrent diabetes, and tipranavir /ritonavir use. A high CD4 count was protective (Crum-Cianflone, et al., 2006). A second study included patients that had been on tenofovir for a period of at least 1 month and showed an

[1] Toxic effect on the kidney
[2] abnormally low amount of phosphate in the blood

elevation in creatinine in 7.3% of patients with hypertension, diabetes, and cardiovascular disease as co-morbidities (Piontkowsky, et al., 2006). A third study indicated that, after a year of treatment with tenofovir, 18.5% of patients developed abnormal renal function, associated only with a low baseline weight. In this last study, no association was found with diabetes or CD4 count (Rocha, et al., 2006). All three studies looked only at patients on tenofovir (no comparator group). Table C below summarizes the toxicity of d4T, AZT, and TDF.

Table C: Summary of toxicity of d4T, AZT, and TDF

ART	Side effect
D4T	Symptomatic hyperlactataemia/ lactic acidosis
	Lipodystrophy
	Peripheral neuropathy
AZT	Anaemia
	Neutropenia
TDF	Renal impairment

4. D4T VS Tenofovir

The primary research conducted into the safety and efficacy of tenofovir in comparison to d4T has been by the 903 Study Group, closely linked to the producer of the drug, Gilead Pharmaceuticals. The 903 Study Group encompasses 602 enrolled patients followed for a period from 9 June 2000 to 30 January 2004. The Study Group participated in studies looking at the efficacy of tenofovir in comparison to d4T as well as the renal safety of tenofovir in comparison to d4T.

Through the Study 903 group, tenofovir has been shown be equivalent to d4T in terms of impact on HIV viral load at 48 and 144 weeks on treatment. In addition, tenofovir is also associated with better lipid profiles and less lipodystrophy (Gallant, et al., 2004).

An area of concern with tenofovir is its effect on renal function. A second Study based on the Study 903 group showed that tenofovir and d4T have similar renal safety profiles in HIV positive treatment- naïve patients with normal baseline

renal function (Izzedine, et al., 2005). In another Gilead Sciences associated study, an evaluation of haematopoietic toxicity showed tenofovir to have lower toxicity than all other NRTIs with the exception of 3TC (Cihlar, et al,., 2002).

A small case control study of 54 patients looked at the effect on lactate levels of switching from d4T to tenofovir. After 3 months on tenofovir, the case group showed a significant decrease in hyperlactataemia and a trend towards lower cholesterol levels (Class, et al., 2004).

5. AZT VS Tenofovir

In a noninferiority study conducted comparing a first line ART regimen of tenofovir and emtricitabine to AZT, 3TC, and EFV, the efficacy and tolerability of tenofovir was proven. At 48 weeks, significantly more patients in the tenofovir group reached and maintained a viral load of less than 400 copies per millilitre, reached and maintained a viral load of less than 50 copies per millilitre, and had a greater increase in CD4 count. In addition, more patients in the AZT group discontinued their ART due to adverse events. Anaemia was the most common cause of stopping AZT treatment but no cases were present in the tenofovir group. While renal side effects are a commonly mentioned concern with tenofovir, both the AZT and tenofovir groups showed similar levels of renal safety (Gallant, et al., 2006).

6. Developing Country Tenofovir Trials

Despite its cost, tenofovir has been accessible in some developing countries through ART trials. These trials have looked at the tolerability of tenofovir in limited resource contexts.

A trial in Thailand was conducted with 100 patients starting on d4T/ddi and changing to tenofovir and 174 naive patients started on tenofovir. The trial indicates that the use of tenofovir is not associated with decreased renal function through a median follow up period of 19.6 weeks (patients initially started on d4T) and 12 weeks (patients started on tenofovir) (Gayet-Ageron, et al., 2006).

In rural Uganda, the AHF/Uganda Cares clinic conducted a retrospective observational study of 1000 patients started on a tenofovir based regimen and 1000 patients started on either AZT and 3TC or d4T and 3TC. All patients were on ART

for a minimum of 72 weeks. The study observed that no incidences of renal failure had been observed in the tenofovir group, and that the number of patients changing regimens was much lower in the tenofovir group, indicating greater tolerability (Okongo, et al., 2006).

7. Cost effectiveness

7.1 Health economics

Health economics studies the allocation of resources in the health care sector. In the theory of perfect competition, the firm is assumed to be a price taker and supply and demand dictates the price of a good. However, the perfect market assumes that the product is homogenous, consumers are rational, there are no externalities, no public goods, perfect information is available, and there are a large number of buyers and sellers to prevent influence of the market. The health care market does not fulfil the definition of a perfect market. In health care there is imperfect information, externalities, public goods, questions of consumer rationality, barriers to entry and exit to the market, risk and uncertainty, and economies of scale and monopolies.

The theories of Welfare Economics seek to describe conditions where social welfare can be maximized through alternative allocations of a good. As the health care market is not a perfect market, resource allocation and price determination cannot be left to demand and supply. The application of this sort of reasoning in Health Economics has tended to take an extra-welfarist approach where the maximization of overall societal welfare or utility is replaced by the maximization of health or health-related utility. Thus in Health Economics, efficiency is often defined in terms of the maximization of health within the health care budget constraint.

Because of the limits of the health care market, in addition to the positive economics of judgements about efficiency, normative economics that takes into account value judgements based on ethical principals should be applied. With this framework, equity should also play a significant role in decision making. The health system should not seek to help only individuals, it should help the entire population that it serves. While equity is subjective, frequently used definitions include equal health, the equal utilization of health services for those of equal need and the equal access to health services for those of equal need.

As more options for facilitating health care become available, greater awareness of scarcity in the market and the need for efficiency develop, and the influence of other governments and donors increases, methods for guiding resource allocation and efficiency are needed. Within the health system market and the decision making combination of positive and normative economics, the economic evaluation of health care programmes assists in choosing between options based on their costs and their outcomes.

7.2 Economic evaluation

All full economic evaluations compare at least two alternatives and evaluate both cost and outcomes for all alternatives. Cost is the value of resources used to produce something while opportunity cost is the benefit sacrificed in using the resource in one programme rather than another programme. Outcomes are generally measured in disease specific units or in generic measures.

Efficiency within economic evaluation can be defined as maximizing health gains with the resources available to health care. There are several measures of efficiency with technical efficiency and allocative efficiency being the most prominent in health economics.

Technical efficiency can be defined as the production of a given quantity of output with the minimum value of inputs. This implies that greater technical efficiency is attained through using the cheapest method of production (Clewer and Perkins 1998). Technical efficiency can be viewed as doing things the right way.

Allocative efficiency on the other hand strives to achieve an overall maximization of the health of society. The value of the output therefore cannot be improved (Clewer and Perkins 1998). Along with efficiency in production, allocative efficiency also implies efficiency in distribution. It answers the question of how resources should be allocated to achieve the desired outcome. In other words, allocative efficiency can be seen as doing the right thing. In the health care sector, the most efficient use of resources occurs when those most in need of health care and the highest capacity to benefit are those that receive it.

If a system is technically inefficient, the inputs can be reallocated to gain greater outputs. However, once the inputs are maximized in terms of outputs, the system reaches the point of Pareto-optimality where there is no scope for efficiency savings. At this point, the system has also reached allocative efficiency. Similarly,

if a system is operating at full allocative efficiency, it implies that it has reached optimal technical efficiency.

In addition to efficiency, economic evaluation can be used to consider the issue of equity. Horizontal equity looks at the proportion of those with a need who receive a service. Those who have equal needs should receive equal levels of service. Vertical equity looks at the extent to which people with unequal health needs should receive unequal levels of service. In order to attain maximum equity, it is often necessary to compromise efficiency.

7.3 Cost effectiveness analysis

Cost effectiveness analysis looks at technical efficiency and asks which of various alternatives for treating the same condition would maximize health gains within the budget allocated to that specific health care programme. An analysis contrasts the costs and outcomes of one or more interventions. Cost effectiveness studies can either compare existing programmes or potential programmes. A comparison of potential programmes, often referred to as a threshold study, determines the potential cost of a programme and the level of outcomes necessary in order to meet standards of cost-effectiveness.

By using the added costs and health outcomes associated with alternative interventions, the cost effectiveness analysis calculates the incremental cost effectiveness ratio (ICER) of one intervention in relation to another. Health outcomes can vary from intermediate outcomes such as viral load suppression in HIV positive individuals to longer term outcomes such as quality adjusted life years (QALYs) (Gold, et al., 1996).

The ICER is calculated by dividing the additional costs of an intervention by the additional outcomes. In a few circumstances, a proposed intervention may be less costly and more effective than the status quo. In these circumstances, the intervention should be the preferred solution. However, in most cases, the alternative interventions are more effective but also more costly than the status quo. In these cases, it is not possible to comment on technical efficiency as any decision to implement the programme to the same quantity of patients would require additional resources. Evaluating whether or not this is the right thing to do would require an assessment of the opportunity cost of moving resources from their current usage to this new programme, which is a question of allocative efficiency.

Chapter 3: Methodology

1. Introduction

This chapter provides a review of relevant methodological literature and describes the methods used to select and calculate costs and outcomes for alternative first line ARV regimens and to determine the cost effectiveness of these options. The options considered are: the status quo use of d4T and AZT, the provision of tenofovir for patients after the development of side effects on d4T and AZT, and the substitution of d4T/AZT with tenofovir in all patients with predisposing factors for the development of specified side effects. Table D below illustrates these treatment options.

Table D: Treatment Options

Option	Starting ART (with no predisposing factors)	Starting ART (with predisposing factors)	Upon developing side effect
Arm 1: Status quo	D4T or AZT	D4T or AZT	D4T, AZT, or Kaletra
Arm 2: Change to TDF upon side effect	D4T or AZT	D4T or AZT	TDF
Arm 3: All predisposing start on TDF	D4T or AZT	TDF	TDF

Included in the calculations are data on patient utilization of health care (including facilities, lab tests, and medicines), side effects of medicines, regimen changes due to side effects, extraordinary utilization of health care due to side effects, treatment failure, and clinical outcome (viral load suppression). As most drug side effects manifest within the first 18 months of treatment, patient inclusion has been limited to the GF Jooste cohort that has accessed ARVs for a full 18-month period, were lost to follow up before 18 months, or died before 18 months.

Despite a continuous scale up of the ARV services, requiring a minimum of 18 months of follow-up meant that this number of patients is limited to 440.

Data on health care utilization, medicines accessed and related issues, as well as clinical outcome for this analysis have been gathered from GF Jooste Hospital, a public sector secondary level institution. Unit costs of health care are derived from studies based at GF Jooste and Khayelitsha primary level clinics. It is assumed that costs for primary, secondary, and inpatient care at these two sites reflect standard South African public health facility standards.

2. Methodology for patient level analyses

2.1 Study population and setting

Patients included in this study reside in the GF Jooste Hospital catchment area. This region includes the "Cape Flats" areas of Gugulethu, Mitchell's Plain, Khayelitsha, Philippi, Nyanga, Manenberg, and Hanover Park. These "townships" represent an intersection of "coloured" and black (predominately Xhosa) communities. Living conditions in these townships vary from basic single-family homes to over-crowded "dorms" to dilapidated "shacks." Access to running water, toilets, and electricity is often limited. Gang violence and drug addiction is particularly rife in the coloured areas and personal safety is often a concern across the entire area.

Through the international organization Medicens Sans Frontiers, Khayeltisha saw the introduction of HIV care into three primary level community health centres (CHCs) in 2000; this service was expanded to include ART in 2001. However, the remaining sections of the GF Jooste catchement area were only able to access ARVs and HIV care in December of 2003 when the Hospital implemented its Infectious Diseases Clinic. Despite GF Jooste's position as a secondary level hospital, due to an absence of adequate primary clinic care, the Infections Diseases Unit (IDU) was created to provide basic primary level HIV care. In August 2004, as the ARVs became available at primary level clinics within the GF Jooste catchement area, a specialist, secondary level infectious diseases clinic (the Infectious Diseases Referral Unit- IDR) was created. This clinic serves as the up-referral site for patients with HIV complications stemming from drug side effects, HIV malignancies, and opportunistic infections. Patients from primary care centres in the catchement area are referred for scheduled appointment days. Medical

officers with extensive experience with complex HIV cases manage referred cases until they are stable enough to be referred back to primary care. Through the IDR, patients have access to regular specialist consultations and more sophisticated diagnostic tools than that available at primary centres.

GF Jooste Hospital was chosen for this research as it was one of the earliest health facilities providing ARV treatment according to Government public sector guidelines. As the primary secondary level hospital for the Cape Town Cape Flats area, it services a representative population of public health care facility users in this area. In addition, comprehensive patient records documenting both primary level (IDU) and, where applicable, secondary level (IDR and inpatient) hospital utilization and outcome are available.

2.2 Study Timeframe and Sample Selection

This study was conducted through a retrospective patient record review of infectious disease unit patients at GF Jooste Hospital. Data were collected between June and December 2008. All naïve patients commencing HAART at GF Jooste's IDU between December 2003 and June 2006 who did not transfer out before 18 months of treatment were included (584 patients). Data were available for 440 of the 584 eligible patients.

2.3 Scope of Costs

The cost effectiveness study should be framed for the intended primary audience of the study. The primary audience is determined to be the relevant decision makers and their areas of interest. The perspective of the study determines which costs and effects to include and how they should be valued. By defining the perspective of the study, the researcher can ensure that all relevant costs are included. As this study is conducted from a provider's perspective, variable and fixed costs of the health care system are included.

The provision of ARV medicine through the public sector requires comprehensive medical care including medicines, laboratory tests, clinical investigations, a range of human resources and skills and other variable resources. It also requires long-term investments into the health sector to maintain quality of care within and outside HIV medicine. Costs in this study and secondary sources cited therefore include both variable and fixed costs. The variable costs include the goods, services including human resources, and inputs that change over the course of the intervention and vary with the level of output. In this study, these costs

include medicines, laboratory tests, and clinical investigations. Fixed costs are costs that do not vary with output over the short run or with the quantity of patients seen. These costs include, among others, buildings and furniture (Clewer and Perkins 1998).

Costs are categorized into total, average, and marginal costs. All of these categorizations relate costs to quantity. The total cost is the sum of the variable and fixed costs to produce a quantity of output. The average cost is the average cost per unit of output or the total cost divided by the quantity. The marginal cost is the extra cost of producing one extra unit of output (Clewer and Perkins 1998). The marginal cost is thus related to the slope of the total cost curve. If the change in total cost is increasing rapidly in relation to greater outputs, the marginal cost will be high. If the change in total cost is increasing slowly in relation to greater outputs, the marginal cost will be low.

In economic evaluation, marginal cost is the appropriate cost statistic to use. However, in practice it is difficult to estimate the marginal cost, with the result that the average total cost is used as a proxy. In cost effectiveness analysis, the incremental cost-effectiveness ratio (the change in costs related to the change in effectiveness) is used to aid decision-making (Clewer and Perkins 1998).

Health care utilization and clinical outcomes were gathered through a retrospective patient record review of the GF Jooste IDU. The costs of lab procedures and antiretrovirals were assumed to be in line with standard public sector tender costs. The unit costs of services including the cost per primary care visit, the cost per IDR visit and the cost per inpatient day were taken from secondary cost analyses previously undertaken on the GF Jooste and Khayelitsha cohorts. For primary level ART services, costs were taken from secondary cost analyses undertaken at three Khayelitsha CHCs and the TC Newman district hospital (Cleary, et al., 2006). Secondary level HIV care costs were derived from a costing study at GF Jooste Hospital (Kevany, et al., forthcoming) and revised to represent the current status of the IDR and wards. In some cases, these cost analyses only collected incremental costs (excluding capital and overheads) while others calculated full economic costs. Adjustments were therefore made to these estimates, again through the use of available secondary data.

Secondary data sources used for costing in this study have included a scope of costs based on average total costs. The costs included in these studies include patient- specific, clinical staff, overhead, capital, and other costs. Table E

below indicates the categories of costs included in the Khayelitsha study that provided cost data for primary care visits and inpatient ward days (Cleary, et al., 2006).

Table E: Scope of costs included in analysis for Khayelitsha study

Health care resources
Patient-specific costs (prophylactic and curative medicines, imaging)
Clinical staff (medical officers and professional nurses)
Overheads (non-clinical staff, running costs)
Capital (equipment, furniture, vehicles, buildings)
Other related resources
Counselling and support groups
Nutritional support

Data from a case study of GF Jooste Hospital's IDR clinic was used to provide cost information for the IDR appointments. Costs included patient-specific and medical staff costs but excluded capital and overheads (Kevany, et al., forthcoming).

2.4 Health Care Utilization

Health care services associated with GF Jooste HIV treatment have been categorized into IDU (primary care), IDR (secondary care), and in-patient stays (secondary care). Data on health care utilization for D4T and AZT users were collected from hospital records as part of this study.

Utilization of clinic visits was established from 440 patients for the follow up period of 18 months. Patients referred to the IDR and wards were followed up through hospital folders.

2.5 Measuring clinical outcomes

As a retrospective study based on a cohort of patients to whom no questions were asked regarding change in lifestyle, health, mobility, self care, or other indicators generally associated with quality of life, it is not possible to analyse

quality adjusted life years (QALYs) for this patient group. It is, however, accepted that a patient's HIV viral load is a good indicator of whether ART treatment is successful (Lawn, et al., 2005; Calmy, et al., 2007). The clinical outcome for this study has, therefore, been determined as viral load suppression on first line ART at 18 months on ARV treatment.

3. Data Collection

GF Jooste patient registers provided a list of all patients commencing ART between December 2003 and June 2006. Available patient folders and hospital records were pulled to provide patient notes for all appointment attendances. A data collection tool was used to note patient baseline information, predisposing factor(s), ART regimen, adverse event(s), management of the adverse event(s), and the outcome of the event(s) for each patient. Data for all appointments including appointment date, patient weight, ART regimen, labs and investigations performed, side effects present, and any outcomes such as change in regimen, loss to follow up, or death were captured for every patient. In addition, the outcome measure for this cost- effectiveness study, undetectable viral load at 18 months on ART, was also captured.

4. Cost and Outcome Analysis

Utilising data collected from this study, patients have been analysed within several cohorts. From these cohorts, the costs and outcomes attributable to each treatment arm have been determined. The costs and outcomes of the status quo have been determined from the data for all 440 patients. The costs and outcomes of the second arm (patients change to TDF based regimens upon developing side effects) were assessed by separating the 440 patients into two cohorts- those that develop side effects that require a change in ART regimen and those that do not. Costs and outcomes for the third arm (all patients with predisposing factors start on TDF) were assessed by separating the 440 patients into two cohorts- those with predisposing factors and those without, and costs and outcomes were then based on the former. In addition, the patients that did not change regimen due to side effects and did not have predisposing factors were analysed as the fifth cohort. Data from this group provided hypothetical cost and outcome data for patients on TDF.

Total costs for each costing category have been assessed for all patients across all visits. For each cohort, average costs per category per quarter and over 18 months were calculated by dividing total cohort costs by the number of patients in the cohort at each time interval. ART costs were calculated based on the number of patients on each regimen at each time interval. Laboratory costs were calculated by dividing the total laboratory costs per quarter by the number of patients active per quarter. Data sorting, cleaning, and analysis was performed using Microsoft EXCEL 2000.

4.1 Accounting for uncertainty

Uncertainty in economic evaluation occurs at numerous levels related to the data requirements of a study as well as the process of evaluation. Briggs and colleagues identified four key sources of uncertainty as methodological disagreement, data requirements, extrapolation of observed results over time, and generalizability to other settings. This paper will only suffer from methodological and generalizability uncertainty as there has been no extrapolation of data or sampling.

Methodological uncertainty in economic evaluation focuses on the debate around a variety of techniques to measure and value health outcomes and costs as well as the decision as to which costs and benefits to include. Because the results of cost effectiveness studies only have meaning in relation to the results of other cost effectiveness studies, a core set of methods allows for better comparison between evaluations. Most 'reference cases' define a set of methods and outcomes of 'cost per life year' and 'cost per QALY'. Sensitivity analyses can also be useful in determining whether the results of a study would change with different methods (Briggs, et al., 2004).

As the reference case is not applicable to this study, the only uncertainty in data that is relevant is the question of discounting. Discounting addresses the preference of spending in the future rather than the present. Studies must decide whether to discount and, if so, how much to discount. This study follows patients for a total of 18 months. As discounting is only implemented after a time period of one year, the effect of discounting would be minimal.

The uncertainty of the data relevant to cost-effectiveness studies and the measurement of ICERs can be dealt with through confidence intervals. However, because the ICER is a ratio, there is added complexity in the calculation of

confidence intervals. Varying theories on calculating the confidence interval include Fieller's theorem, bootstrapping, and the Monte Carlo simulation. These methods are useful for ICERS that have significantly positive numerators and denominators (the intervention is more costly and more effective). In cases where the ICER is not significantly large in either numerator, denominator, or both, added complications arise. As the ICER tends towards zero, the uncertainty rises rapidly. In these circumstances, the uncertainty of the ICER can be calculated through acceptability curves or the net-benefit framework. The acceptability curve graphs the possible cost of the programme against the probability of the programme being cost-effective. For every cost, it therefore summarizes the evidence in favour of cost-effectiveness as well as provides information for the confidence interval on cost-effectiveness. The net-benefit framework rearranges the decision rule for cost-effectiveness analysis to create a linear expression. This allows the net-benefit to be plotted as a function of the cost. The net –benefit curve crosses the horizontal axis at the point of estimated cost-effectiveness of the intervention. The confidence curves cross the axis at the high and low ends of the confidence interval on cost-effectiveness (Briggs, 2001).

In cost-effectiveness studies where the cost and outcome data are synthesized from existing evidence (rather than directly observed), parameters are created to guide the model. In these cases, there are known and unknown parameters. Unknown parameters could be the probability of moving from one state to another over time and the costs and consequences of an intervention. Parameters are considered to be random variables and, in dealing with uncertainty, their values can be along the range of a determined distribution. This distribution is selected to account for the uncertainty in the parameter rather than the variability in the population. Acceptability curves can also be used to compare between multiple options.

The generalizability of this study to other settings has been assessed by comparing reports of side effects to other published cohorts in low income countries (Okongo, et al., 2006; Gayet-Ageron, et al., 2006). Inpatient and visit utilization data have been compared to the South African National Antiretroviral Treatment Guidelines 2004 for follow up of patients on ART. Unit costs are taken from published secondary sources and official tender prices. Outcomes have been compared to a range of developing world cohorts.

Uncertainty in economic evaluation can be assessed using different types of sensitivity analysis. These forms include simple sensitivity analysis, threshold analysis, and probabilistic sensitivity analysis.

Simple sensitivity analysis involves varying one or more parameters one at a time within a plausible range while the other parameters remain at their set values. This allows the investigator to determine the effect of variations in parameters on the result. Multi way sensitivity analysis involves varying two or more parameters at the same time. This is useful in analysing hypothetical scenarios that involve changes in several factors at once. For example, patients in the study cohort have access to secondary and tertiary care for side effect management. However, in other settings, these specialist institutions may not be available and palliative side effect management may not be available. A scenario that reflects this situation would vary the costs of specialist care as well as loss to follow up rates. Threshold analysis can also be used to determine at what parameter levels and combinations certain treatment options become cost neutral or cost saving.

Probabilistic sensitivity analysis involves assigning each parameter a distribution of values. Random values are selected from these distributions in a Monte Carlo simulation of the model to generate cost-effectiveness results. This type of simulation captures variability in the parameter of interest rather than variability in the underlying population.

In this thesis, a simple sensitivity analysis varying the percent of patients on TDF with viral load suppression has been conducted. Furthermore, secondary source data on the TDF viral suppression was used to assess the outcomes associated with the TDF arm. The change in outcome per arm and ICERs were calculated. Threshold analyses were performed on the ICERs with secondary source data for TDF viral suppression. These analyses determined prices at which the two alternative treatment arms become cost neutral and cost saving.

5. Ethical Issues

The University of Cape Town's Research Ethics Committee approved the primary research on which this thesis is based. The Infectious Diseases unit manager and the GF Jooste Hospital Ethics Committee approved access to GF Jooste Hospital facilities and patient records.

6. Summary

This chapter has described the methodology that will be used in later chapters to calculate patient level costs and outcomes in alternative first line ART treatment regimens. Uncertainty will be addressed using simple sensitivity analysis and threshold analysis. Through data analysis, it will be possible to assess the health gains and costs associated with the four first line ART treatment options and to determine threshold costs at which TDF becomes cost effective for each option.

Chapter 4: Results

1. Introduction

This chapter describes the total costs and outcomes of the three treatment options over an eighteen-month period. Costs are set at September 2008 price levels and outcomes are presented as percent of patients on first line ART with viral suppression at 6, 12, and 18 months of ART therapy.

Costs include facility utilization (i.e. both primary and specialist outpatient care, and inpatient care) laboratory investigations, and ART drug costs.

The original 440 patients were first divided into those who changed ART regimens due to side effects and those who did not have any change in regimen due to side effect. Data from this analysis were used to calculate costs and outcomes for the second treatment arm (patients change to TDF once they develop side effects).

The 440 patients were then analysed in two separate combinations. Patients were first divided into those with predisposing factors for side effects and those without predisposing factors. Data from this analysis were used to calculate costs and outcomes for the third treatment arm (all patients with predisposing factors start on TDF).

A third analysis was performed on the patients who did not have predisposing factors and did not develop side effects. This last group was named 'remainder.' Data from this group were used to calculate costs and outcomes for TDF.

The ICERs for the three treatment arms and the threshold cost for each arm to be cost-neutral has been calculated.

2. Unit costs

Unit cost information for primary level infectious disease visits, capital cost data and unit cost information for inpatient days at GF Jooste Hospital were obtained from a secondary cost analysis previously undertaken on the Khayelitsha cohort (Cleary, et al., 2006). Operational unit cost data for Infectious Diseases

Referral visits was compiled from a 2005 costing of the IDR Unit (Kevany, et al., forthcoming).

Lab costs were obtained from the National Health Laboratory Services (NHLS) State Price List 2008. Table F shows the costs of common investigations performed with HIV patients. Viral load, liver function, and lactate tests are the most costly investigations. Viral load tests are performed for regular monitoring. In cases where a patient is suspected of failing ART treatment or after treatment interruptions, additional viral load tests are done to ensure appropriate HIV management. Patients on NVP have safety liver function tests done at two weeks on treatment. Other than this safety test, liver function and lactate tests are done only for patients suspected of developing side effects to ART. Management and treatment for side effects requires additional tests.

Table F: Costs for laboratory investigations

Laboratory Investigation	**Cost (Sept 2008 South African Rand)**
Full blood count	45.57
Haemoglobin	14.18
White Cell Count	14.18
Differentials	24.99
Platelets	16.80
Liver Function Tests	200.45
ALT	35.70
ALP	34.02
Lactate	106.89
Creatinine	23.84
CEU	95.36
Lip	34.34
CD4	60.00
Viral load	300.00
Glucose	23.84
Triglycerides	52.61
Cholesterol	35.49
Hepatitis B	98.91
CRP	71.51
Potassium	12.84
Sodium	23.84
Urea	23.84
CK	38.12
CSF	182.09
Iron	53.66
Albumin	31.61
Blood gas	42.53
AST	35.70

ART costs were obtained from the ARV Depot price list for 2008. At present, the standard first line ART drugs used in South Africa are stavudine (d4T), zidovudine (AZT), lamivudine (3TC), efavirenz (Efv), and nevirapine (NVP). Four combinations of these drugs comprise South Africa's basic triple-therapy first line ART regimens. These first line regimens are d4T/3TC/Efv, d4T/3TC/NVP, AZT/3TC/Efv, and AZT/3TC/NVP. The alternative first line regimen considered in this thesis is tenofovir (TDF) and Efv. When a patient is no longer virally suppressed on a first line regimen, he/she is switched to second line ARV treatment. The standard second line regimen in South Africa is Kaletra/AZT/ddI. However, a patient may also be put on dual therapy of Kaletra and Efv or mono therapy of Kaletra only. Table G below indicates the cost per month of the ART regimens. The cost of Kaletra makes second line ART management significantly more costly than first line treatment.

Table G: Costs per ART regimen

Regimen	**Cost per month (Sept 2008 SA Rand)**
D4T / 3TC/ Efv	171.93
D4T / 3TC / NVP	83.53
AZT / 3TC / Efv	128.34
AZT / 3TC / NVP	216.74
Kaletra / Efv	515.61
Kaletra	394.07
Kaletra / AZT/ddI (250mg if <60kg)	632.28
TDF / Efv	288.31

2.1 Adjustments to costs

All data were adjusted to September 2008 price levels using the South African CPIX rate. Data from Cleary were converted from US Dollars to South African Rand at the rate indicated in the study prior to adjusting for inflation. Table H below indicates the cost of outpatient and inpatient visits. The general cost function used to calculate these costs was;

$$\text{Total cost} = \text{Cost}_{\text{drugs}} + \text{Cost}_{\text{laboratory investigations}} + \text{Cost}_{\text{appointments}} + \text{Cost}_{\text{ward day}}$$

The rise in cost between standard primary appointments and referral management reflects the increase in resource utilization for complications resulting

from ART side effects and opportunistic infections. As complications also lead to an increase in frequency of appointments, the cost of referral management is amplified. Cases requiring inpatient stays further increase the cost of patient care.

Table H: Costs per appointment type and ward day

Appointment type	**Cost (Sept 2008 South African Rand)**
Primary level ID appointment	201.05
GF Jooste IDR appointment	795.11
GF Jooste Ward day	1230.97

3. Outcome analysis

The first treatment arm in this thesis has patients being initiated onto d4T or AZT based first line regimens. Patients that develop side effects are managed according to the current status quo. The 440 patients were therefore analysed as a whole to yield data for the costs and outcomes of this arm.

The second treatment arm starts patients on d4T or AZT based regimens. Upon development of side effects requiring a change in regimen, patients are changed to TDF. In order to obtain data to guide the costs and outcomes of this arm, the 440 patients were separated into two cohorts. The first cohort includes all patients that develop side effects requiring a change in ART regimen ("side effects"). The second cohort includes patients that do not develop side effects or develop side effects that do not require a change in ART regimen ("no side effects").

The third treatment arm in this thesis starts all patients with predisposing factors for ART side effects on a TDF based regimen. All patients without predisposing factors would be started on the standard South African first line ART treatment. While there are several predisposing factors for d4T and AZT side effects, this thesis is concerned with side effects that lead to a change in ART regimen. Factors associated with minor side effects such as peripheral neuropathy and anaemia have not been included. The predisposing factors that are included are those that are associated with the development of lactic acidosis- weight at ART initiation greater than 60 kg and female gender (Osler, et al., forthcoming).

In order to obtain data that guides the cost and outcome calculations for this second arm, the 440 patients were separated into two cohorts. The first cohort included all patients with predisposing factors for side effects ("predisposing"). The second cohort included all patients without predisposing factors for side effects ("non predispose"). Costs and outcomes are therefore calculated as a weighted average from these two groups.

Data for the costs and outcomes of TDF are not available in developing world settings. This thesis uses a subset of the total patients to inform calculations of costs and outcomes for the patients that would be on TDF based regimens. These data are calculated from the cohort of patients that do not have predisposing factors and do not develop side effects ("remainder"). Throughout this thesis, when a patient is placed on TDF, all cost and outcome data is sourced from this 'remainder' cohort. In arm 2, the costs and outcomes are attributed once patients change regimen due to side effects. In arm 3, these costs and outcomes are attributed to all patients in the "predisposing" cohort as they would be initiated on TDF therapy. A detailed definition of each of these cohorts is presented below.

1. TOTAL- All patients who were ART naïve and started ART treatment at GFJ between Dec 2003 and June 2006. Patients who transferred out before 18 months of treatment were excluded
2. NO SIDE EFFECTS- Of the total patients, patients who did not change ART regimen due to side effects during their 18 months of treatment
3. SIDE EFFECTS- Of the total patients, patients who changed ART regimen due to side effects during their 18 months of treatment
4. NON PREDISPOSE- Of the total patients, patients who did not have any of the predisposing factors
5. PREDISPOSING- Of the total patients, patients who had predisposing factors
6. REMAINDER- Of the total patients, patients who did not have predisposing factors and did not develop side effects

Table I below illustrates the gender composition of the various cohorts. Approximately one-third of all patients are male. Males comprise slightly less than

one-third of those patients who develop side effects. As female gender is a predisposing factor for lactic acidosis, all females are included in the predisposing cohort.

Table I: Cohort Makeup

Cohort	Males	Females	Total
Total	157	283	440
No Side Effect	117	189	306
Side Effect	40	94	134
No Predisposing	77	0	77
Predisposing	80	283	363
Remainder	61	0	61

Table J demonstrates the breakdown of the total patient group. A two-tailed chi- squared test shows that, between the 'predisposing' and 'no predisposing' cohorts, the proportion of patients developing side effects is not significantly different (P=0.0581).

Table J: Cross Tabulation Illustrating Cohort Groups

	Side Effect	No Side Effect	Total
Predisposing	118	245	363
No Predisposing	16	61	77
Total	134	306	440

3.1 Data Analysis

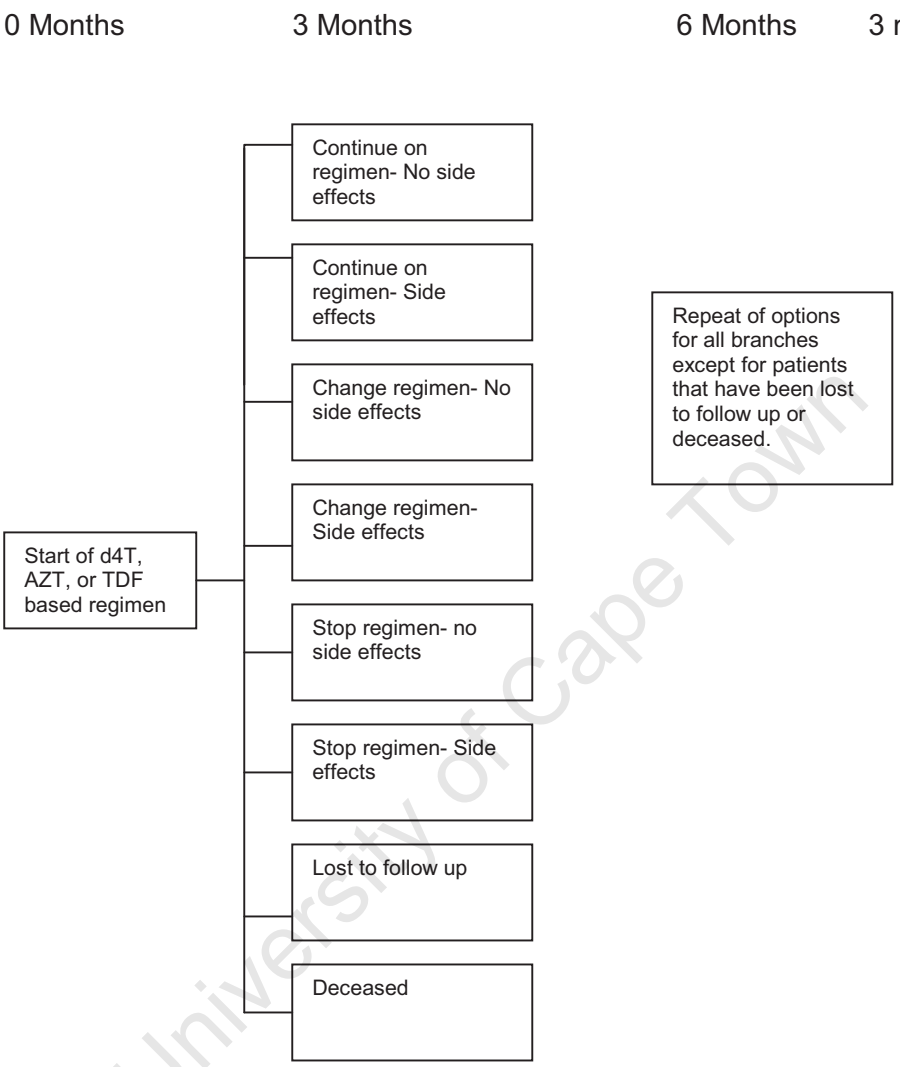
Data were analysed in three monthly intervals. Appointments that resulted in ward admissions were classified as IDR appointments. Utilization data and side effect occurrence was noted per patient. At each three monthly interval, patients were classified as either continuing on their ART treatment, changing ART treatment, stopping ART treatment, becoming lost to follow up, or dying.

Patients in arm 1 (status quo) would flow through this basic decision tree until they reached an end stage or eighteen months of treatment.

Patients in arm 2 (patients change to a TDF based regimen upon developing side effects requiring a change) would all start on d4T or AZT regimens but would change to TDF regimens as soon as a change was needed.

Patients in arm 3 (predisposing patients start on TDF regimen) would also flow through this basic decision tree. The primary difference would be that the starting regimen at time zero would be TDF based for all those with predisposing factors. In addition, patients without predisposing factors requiring a change of regimen would 'change regimen' to a TDF based regimen as opposed to a d4T or AZT based regimen.

Diagram A: Basic decision tree of model



3.2 Outcomes

The effectiveness of ART therapy in controlling the HIV virus is monitored by testing the viral load of HIV in a patient's blood. In South Africa, viral load testing occurs at six monthly intervals. A rise in viral load above the undetectable limit of 400 copies per millilitre indicates that the patient's ART regimen is no longer suppressing the HIV. Viral load suppression is an indicator of whether ART is successful (Lawn, et al., 2005; Calmy, et al., 2007). The percent of patients virally suppressed is the outcome measure for this thesis.

For each cohort, the number of patients continuing on first line ART with viral suppression at six, twelve, and eighteen months was captured. Viral load tests were allocated to the closest six-month interval. Viral load suppression rates were calculated among those with viral load test. As seen in Table I, viral load suppression rates are highest for the side effect and predisposing cohorts. However, the differences in outcome are not statistically significant. The difference could be explained by more vigilant monitoring by medical officers, patient management by the GF Jooste IDR clinic, or self selection (patients with side effects that stay in care rather than become lost to follow up may be more adherent). Table K below provides the number of patients with viral loads lower than detectable in relation to the total number of patients in the cohort, the percent of patients, and the confidence intervals.

Table K: Outcomes by cohort

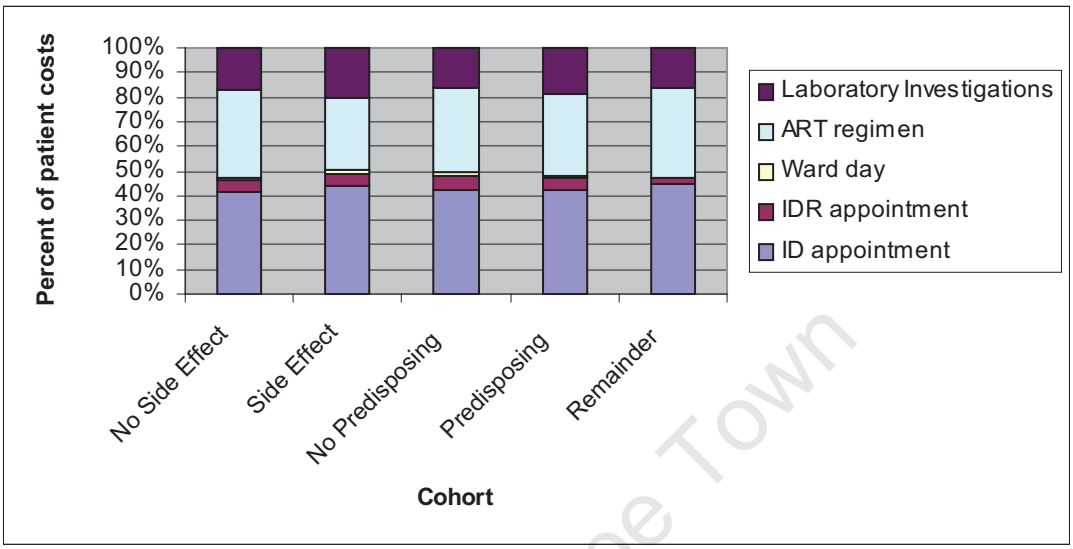
	Total	**No Side Effect**	**Side Effect**	**Non predispose**	**Predispose**	**Remainder**
VL lower than detectable level at 6 months	296/317 93.4 (90.7, 96.1)	190/204 93.1 (89.6, 96.6)	106/113 93.8 (89.4, 98.2)	49/53 92.5 (86.4, 99.6)	247/264 93.6 (90.6, 96.6)	37/41 90.2 (81.1, 99.3)
VL lower than detectable level at 12 months	245/270 90.7 (86.2, 94.2)	156/175 89.1 (84.5, 93.7)	89/95 93.7 (88.8, 98.6)	42/48 87.5 (78.1, 96.9)	203/222 91.4 (87.7, 95.1)	32/36 88.9 (78.6, 99.2)
VL lower than detectable level at 18 months	226/261 86.3 (82.1, 90.5)	143/166 86.1 (80.8, 91.4)	83/96 86.6 (79.8, 93.4)	39/46 84.8 (74.4, 95.2)	187/216 86.6 (82.1, 91.1)	31/36 86.1 (74.8, 97.4)

3.3 Utilization of health services

For all cohorts, the utilization that leads to the greatest cost burden is primary level appointments. Across all time periods, the cost of medical appointments accounts for nearly half of all patient costs. There is a marked peak

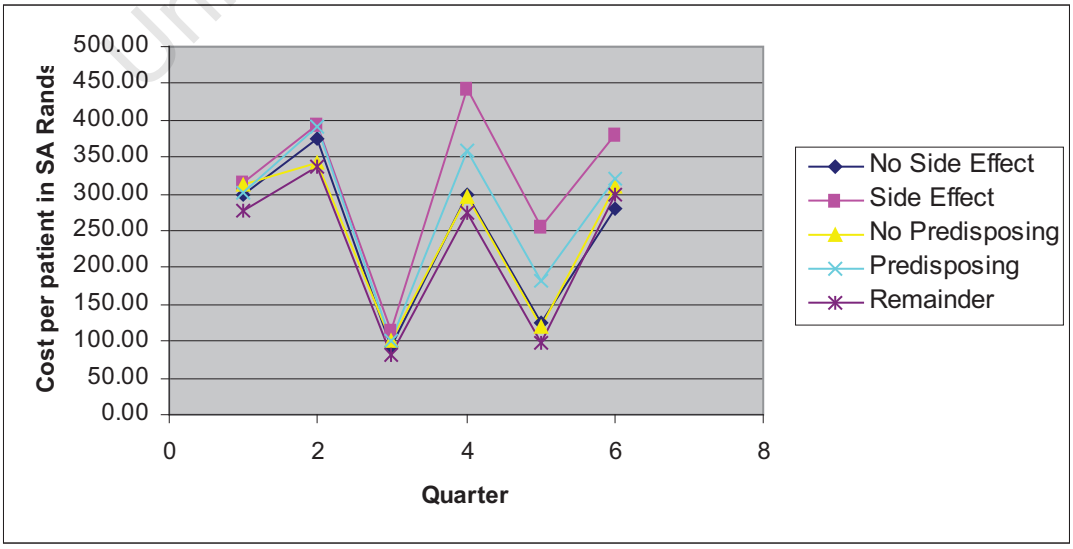
in utilization in the first three months of ART care. Chart A, below, shows the distribution of total costs per cohort by category.

Chart A: Total Cost Per Cohort



The consistent factor that yields higher costs for those who develop side effects is laboratory investigations. Chart B below illustrates the cost of laboratory investigations per cohort over six quarters.

Chart B: Cost of Laboratory Investigations by Cohort



The ‘no side effect’ and ‘predisposing’ cohorts had the greatest proportion of patients started on AZT based regimens. As medical officers are aware of the predisposing factors for d4T side effects, they try to start patients with predisposing factors on AZT. This explains the greater proportion of patients on AZT in the ‘predisposing cohort.’ As AZT has fewer side effects than d4T, patients on AZT are more likely to fall into the ‘no side effect’ cohort. This discrepancy may have an impact on the outcomes of the cohorts. As AZT is more expensive than d4T, this results in the ARV drug costs for the ‘no side effect’ cohort being greater than the costs for the ‘side effect’ cohort. Despite the higher drug costs, the ‘no side effect’ cohort is less costly than the ‘side effect’ cohort in five of the six quarters. Excluding the cost of ART results in the ‘side effect’ cohort being more costly throughout the study period. The breakdown of patients per regimen by cohort can be seen in Table J.

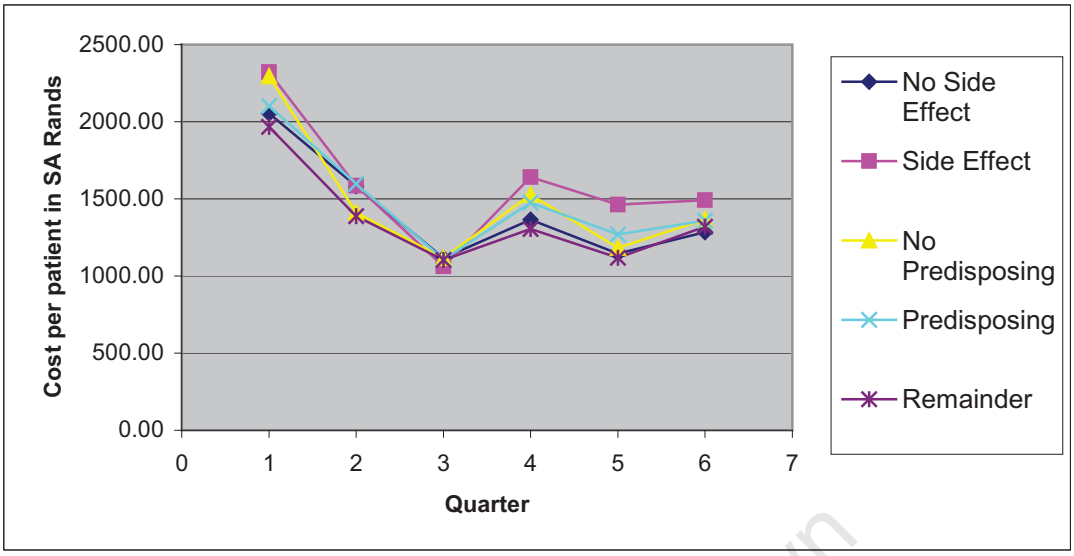
Table L: Starting ART regimen per cohort

ART Regimen	Total	No Side Effect	Side Effect	Non Predispose	Predispose	Remainder
d4T/3TC/Efv	296	201	95	64	232	51
d4T/3TC/NVP	76	49	27	2	74	2
AZT/3TC/NVP	31	29	2	0	31	0
AZT/3TC/Efv	27	23	4	8	19	6
Unknown d4T based	10	4	6	3	6	2

In order to conduct costing, regimens classified as ‘unknown d4T’ were allocated to d4T/3TC/Efv. In Table J above, original data, with the unknown d4T regimens in the last row, is presented. The second line regimens Kaletra plus two drug regimens were classified as Kaletra/ddI/Efv as this is the standard second line regimen. Kaletra plus one drug regimens were classified as Kaletra/Efv.

Over time, the total cost for patients who develop side effects increases over the other cohorts. Chart C shows the trend of total cost per patient by cohort over six quarters. It can be seen that the ‘no side effect’ and ‘remainder’ cohorts have the lowest per patient cost by quarter six while the ‘side effect’ cohort has costs R200 per quarter higher the ‘no side effect’ cohort.

Chart C: Cost Per Quarter by Cohort



The combined utilization of medical appointments, ART regimens, and laboratory investigations by cohort is documented in Table M below. Appointment costs account for approximately two-thirds of the total costs for all cohorts in the first quarter. Thereafter, they comprise approximately half of the total costs. The spikes in laboratory investigation costs at quarters 2, 4, and 6 reflect regular monitoring tests. A more detailed version of Table M can be found in Appendix 1.

Table M: Utilization of health resources by cohort (cost per patient in SA Rands Sept 2008)

Utilization summary	Total	No Side Effect	Side Effect	No Predisposing	Predisposing	Remainder
Quarter 1						
All appointments	1362.46	1287.45	1545.17	1486.77	1336.09	1195.67
ART and laboratory costs	760.57	767.06	776.77	808.15	766.19	771.91
Total quarter 1	2123.03	2054.52	2321.93	2294.92	2102.28	1967.58
Quarter 2						
All appointments	695.22	695.69	727.24	591.49	716.97	572.80
ART and laboratory costs	848.80	887.74	858.28	819.68	880.65	815.43
Total quarter 2	1544.02	1583.43	1585.52	1411.17	1597.62	1388.23
Quarter 3						
All appointments	535.53	537.31	532.10	543.88	535.43.95	544.98
ART and laboratory costs	559.97	579.27	529.19	573.29	572.00	558.93
Total quarter 3	1095.51	1116.58	1061.29	1117.18	1107.43	1103.91
Quarter 4						
All appointments	647.57	554.35	755.58	758.42	624.22	547.25
ART and laboratory costs	836.48	810.62	885.47	769.21	850.65	756.93
Total quarter 4	1484.05	1364.98	1641.05	1527.63	1474.87	1304.18
Quarter 5						
All appointments	550.28	482.56	683.77	536.13	553.32	514.69
ART and laboratory costs	703.81	663.30	779.06	645.91	716.21	603.37
Total quarter 5	1254.09	1145.86	1462.83	1182.04	1269.53	1118.06
Quarter 6						
All appointments	490.94	461.04	547.04	531.83	482.26	514.45
ART and laboratory costs	865.83	823.52	944.99	835.66	876.10	805.48
Total quarter 6	1356.77	1284.56	1492.03	1367.49	1358.35	1319.93
18 month total	**8857.47**	**8549.92**	**9564.66**	**8900.43**	**8910.10**	**8201.89**

4. Treatment Arms Cost and Outcomes

The cost, utilization and outcome data from the six cohorts provides the framework for concluding the cost effectiveness of the three treatment arms. As the

side effect profile of TDF is minimal, patients on TDF will have costs associated from the "remainder cohort."

4.1 Costs per arm

4.1.1 Arm 1 Costs

As arm one is the status quo, the total cost of arm one is the same as the total cohort cost.

Arm 1 (current protocol)

> Total cost= Total cost of cohort "Total"

Costs for arm 1 would therefore be the same as the 'total' cohort, R8857.47 per patient over 18 months.

4.1.2 Arm 2 Costs

In arm 2, patients that do not develop side effects requiring a change in regimen will have the costs of the "no side effects" cohort. Patients that do develop side effects requiring a change in regimen will have costs from the "side effects" cohort until the regimen change. After the regimen change, these patients will have the costs of the "remainder" cohort. The cost of TDF is substituted for the remainder ART regimen costs.

Arm 2 (patients who develop side effects switch to Tenofovir)

> Total cost= ∑ from q1 to q6 ((Average cost per patient in NO SIDE EFFECTS * number of patients in NO SIDE EFFECTS) + (Average cost per patient in SIDE EFFECTS * number of patients in SIDE EFFECTS who have not yet developed the side effect) + (cost TDF * number of patients who have developed side effects by beginning of quarter) + (average cost per patient in REMAINDER * number of patients who have developed side effects by beginning of quarter)

The 306 patients that do not develop side effects have a cost of R8549.92 per patient over 18 months.

Costs for patients that develop side effects are as follows:

Twenty-four of 134 patients change regimen at the end of quarter 1. These patients have the "remainder" cohort costs, excluding ART, for quarters 2 through 6 of R3782.85 in addition to the quarter 1 "side effect" cohort costs of R2321.93. The TDF regimen costs for quarters 2 through 6 totals R4324.65.

Twenty-six of 134 patients change regimen at the end of quarter 2. These patients have “remainder” cohort costs, excluding ART, for quarters 3 through 6 of R2873.12 in addition to quarters 1 and 2 “side effect” cohort costs of R3907.45. The TDF regimen costs for quarters 3 through 6 totals R3459.72.

Twenty-five of 134 patients change regimen at the end of quarter 3. These patients have “remainder” cohort costs, excluding ART, for quarters 4 through 6 of R2247.00 in addition to quarters 1 through 3 “side effect” cohort costs of R4968.75. The TDF regimen costs for quarters 4 through 6 totals R2594.79.

Thirty-six of 134 patients change regimen at the end of quarter 4. These patients have “remainder” cohort costs, excluding ART, for quarters 5 and 6 of R1424.99 in addition to quarters 1 through 4 “side effect” cohort costs of R6609.80. The TDF regimen costs for quarters 5 and 6 totals R1729.86.

Sixteen of 134 patients change regimen at the end of quarter 5. These patients have “remainder” cohort costs, excluding ART, for quarter 6 of R813.43 in addition to quarters 1 through 5 “side effect” cohort costs of R8072.63. The TDF regimen costs for quarter 6 is R864.93.

The 7 patients that change at the end of quarter 6 have “side effect” cohort costs for all quarters of R9564.66.

The patient cost for those that develop side effects in arm 2 is therefore R9972.49 over 18 months.

The weighted patient cost for arm 2 is R8983.16. Table N below summarizes these costs per quarter. Pre side effect quarter costs are in italics. Costs per quarter after side effect, excluding cost of TDF are in normal font. Total TDF costs are indicated under “TDF costs.”

Table N: Arm 2 Calculation of costs for patients that change regimen due to side effects

Quarter of First Regimen Change	Number of patients	Q1 cost	Q2 cost	Q3 cost	Q4 cost	Q5 cost	Q6 cost	TDF costs	Total cost per patient	Total (number of patients * cost per patient)
No change	306	*2054.52*	*1583.43*	*1116.58*	*1364.98*	*1145.86*	*1284.56*	*0.00*	8549.92	2616275.52
Q1	24	*2321.93*	909.72	626.12	822.01	611.56	813.43	4324.65	10429.43	250306.3
Q2	26	*2321.93*	*1585.52*	626.12	822.01	611.56	813.43	3459.72	10240.29	266247.6
Q3	25	*2321.93*	*1585.52*	*1061.29*	822.01	611.56	813.43	2594.79	9810.54	245263.4
Q4	36	*2321.93*	*1585.52*	*1061.29*	*1641.05*	611.56	813.43	1729.86	9764.65	351527.3
Q5	16	*2321.93*	*1585.52*	*1061.29*	*1641.05*	*1462.83*	813.43	864.93	9750.99	156015.8
Q6	7	*2321.93*	*1585.52*	*1061.29*	*1641.05*	*1462.83*	*1492.03*	0.00	9564.66	66952.63
						Arm 2 patient cost			9972.49	

4.1.3 Arm 3 Costs

In arm 3, the patients without predisposing factors will have the costs of the "non predispose" cohort. Patients with predisposing factors will be started on TDF and will have the costs from the "remainder" cohort. The cost of TDF is substituted for the ART cost in the remainder cohort.

Arm 3 (patients with predisposing factors start on Tenofovir)

> Total cost= ∑ from q1 to q6 ((Average cost per patient in NON PREDISPOSE * number of patients in NON PREDISPOSE) + ((cost TDF * number of patients in PREDISPOSE) + (Average cost per patient in REMAINDER * number of patients in PREDISPOSE))

The 77 patients without predisposing factors have a cost of R8900.43 per patient over 18 months.

The remaining 363 patients with predisposing factors have a TDF ART regimen cost of R864.93 per quarter or R5189.58 per 18 months. The other costs from the "remainder" cohort total R5256.19 per 18 months. The total cost for patients with predisposing factors would then be R10445.77.

The weighted patient cost for the cohort would be ((77/440) * R8900.43) + ((363/440) * R10445.77) or R10175.34 per patient over 18 months.

4.2 Outcomes per arm

4.2.1 Arm 1 outcomes

As seen in Table G above, of patients in the cohort at the beginning of each six-month interval, 93.4% (0-6 months), 90.7% (6-12 months), and 86.3% (12-18 months) of patients were on first line ART and had undetectable viral loads.

4.2.2 Arm 2 outcomes

The 306 patients that do not develop side effects resulting in a change of ART regimen would have the outcomes of the 'no side effects' cohort. The outcomes would therefore be 93.1%, 89.1%, and 86.1% of patients on first line ART with undetectable viral loads at 6, 12, and 18 months.

The 134 patients that develop side effects and change regimen would have outcomes related to the 'side effects' cohort before they change regimen and the outcomes of the 'remainder cohort' after their change of regimen. Patients that develop side effects and change regimen more than once are assigned to change to TDF regimens on the first change of regimen.

According to Table N above, 24 patients changed ART regimen in the first quarter, 26 in the second, 25 in the third, 36 in the fourth, 16 in the fifth, and 7 in the last quarter. The outcomes for these patients would be calculated as shown in Table O below.

Table O: Arm 2- Outcome allocation

Change in	Outcome 0-6 months	Outcome 6-12 months	Outcome 12-18 months
Quarter 1	Side effect cohort	Remainder cohort	Remainder cohort
Quarter 2	Side effect cohort	Remainder cohort	Remainder cohort
Quarter 3	Side effect cohort	Side effect cohort	Remainder cohort
Quarter 4	Side effect cohort	Side effect cohort	Remainder cohort
Quarter 5	Side effect cohort	Side effect cohort	Side effect cohort
Quarter6	Side effect cohort	Side effect cohort	Side effect cohort
No Change	Side effect cohort	Side effect cohort	Side effect cohort

The six-month outcome for this group of arm 2 would therefore be the same as that for the side effect cohort or 93.8% of patients on first line ART with undetectable viral loads. At twelve months the 50 patients that switch regimens in quarter one or two will have an outcome of 88.9% while 84 will have an outcome of 93.7%. At eighteen months, the 111 patients that change regimen in quarters one through four will have an outcome of 86.1% while the remaining 23 patients will have an outcome of 86.46%.

This yields outcomes of 93.3%, 90.0%, and 86.2% of patients on first line ART with undetectable viral loads as indicated in Table P.

Table P: Outcome Summary- Viral load suppression for Arm 2

Arm 2 Outcome Summary				
Patient group	number of patients	6 month viral load suppression	12 month viral load suppression	18 month viral load suppression
no side effects	306	93.1	89.1	86.1
side effects q1 and q2	50	93.8	88.9	86.1
side effects q3 and q4	61	93.8	93.7	86.1
side effects q5 and q6	23	93.8	93.7	86.5
Total weighted outcome		**93.3**	**90.0**	**86.2**

4.2.3 Arm 3 outcomes

The 363 patients with predisposing factors would be started on TDF based regimens and are assumed to have outcomes similar to the 'remainder' cohort. At six, twelve, and eighteen months, this group would therefore have 90.2%, 88.9%, and 86.1% of its patients on first line ART with undetectable viral loads.

The remaining 77 patients would have the outcomes of the 'non predisposing' cohort with 92.5%, 87.5%, and 84.8% of the patients on first line ART with undetectable viral loads.

Proportionally, the outcomes would be ((363/440) * $outcome_{remainder}$) + ((77/440) * $outcome_{non\ predispose}$) for each six- monthly interval. This yields outcomes of 93.4%, 90.8%, and 86.3% for the arm. These outcomes are summarized in Table Q below.

Table Q: Outcome Summary- Viral Load Suppression for Arm 3

Arm 3 Outcome Summary				
patient group	number of patients	6 month viral load suppression	12 month viral load suppression	18 month viral load suppression
predispose	363	90.24	88.9	86.1
non predispose	77	92.45	87.50	84.78
total weighted outcome		**90.63**	**88.65**	**85.88**

4.3 Results of Cost Effectiveness Analysis

Table R below summarizes costs and outcomes for the three arms. The costs per patient are highest in arm 3 and lowest in arm 1. The outcomes are best in arm 1 and worst in arm 3. However, the outcomes are not statistically significant in difference, as shown by the confidence intervals surrounding these estimates.

Table R: Summary of costs and outcomes per arm

Arm	Cost per patient (SA Rands Sept 2008)	Outcome at 6 months (percent virally suppressed, 95% CI)	Outcome at 12 months (percent virally suppressed)	Outcome at 18 months (percent virally suppressed)
Arm 1 (status quo)	8857.47	93.4 (91.1, 95.7)	90.7 (88.0, 93.4)	86.3 (83.0, 89.5)
Arm 2 (change to TDF once develop side effect requiring ART change)	8983.16	93.3 (91.0, 95.7)	90.0 (87.2, 92.8)	86.2 (82.9, 89.4)
Arm 3 (all with predisposing factors start on TDF)	10175.34	90.6 (88.3, 93.0)	88.65 (85.9, 91.4)	85.9 (82.7, 89.1)

As there is no significant difference in outcome, it is not possible to calculate an ICER for the alternative treatment arms. The status quo is both less costly and equally effective as the alternatives. These results will be further unpacked using sensitivity analysis.

4.4 Threshold Prices for TDF

Arm 2 would become cost neutral at a TDF price of R240.68 per month. This is 83.5% of the R288.31 price used in this study. Arm 3 would become cost neutral at a TDF price of R199.40 per month. This is 69.2% of the price used in this study.

4.5 Simple Sensitivity Analysis

Given the lack of data on the effectiveness of TDF in viral suppression, simple sensitivity analyses were conducted exploring a range of rates of viral load suppression among patients on TDF, using data from published prospective cohort studies. The first study compared patients on a regimen of TDF, lamivudine, and

efavirenz with patients on stavudine, lamivudine, and efavirenz (Study 903 Group). The second compared patients on a regimen of TDF, emtricitabine, and efavirenz to patients on fixed-dose zidovudine, lamivudine, and efavirenz (Study 934 Group). While most of the patients in this study are started on a d4T-based regimen, comparing outcomes to AZT regimens is also useful.

The Study 903 Group comparing a TDF regimen to a d4T regimen had viral load suppression rates for the cohorts at 12 and 24 months. The 24 month data were used in 18 month sensitivity analysis in this study. At 12 months, 239 of 299 patients in the TDF cohort were viralogically suppressed with viral loads under 400 copies per millilitre (79.9 percent) while 253 of 301 patients in the d4T cohort were suppressed (84.1 percent). Those there was a significant difference in viral suppression at 400 copies per millilitre, TDF and d4T were shown to be equally effective in suppressing HIV viral load at the 50 copies per millilitre level (TDF% vs d4T%). At 24 months, 226 of 299 patients in the TDF cohort were viralogically suppressed (75.6%) while 214 of 301 patients in the d4T cohort were suppressed (71.1 percent) (Gallant, et al., 2004).

The Study 934 Group comparing a TDF regimen to an AZT regimen had viral load suppression rates for the cohorts at the 12 month time interval only. At 12-months, 206 of the 244 patients in the TDF cohort had viral load levels of less than 400 copies per millilitre (84 percent) while 177 of the 243 patients on the AZT cohort were viralogically suppressed (73 percent) (Gallant, et al., 2006).

The rates of viral suppression for the TDF cohorts and the AZT and d4T cohorts from Study 903 and 934 were substituted for the outcomes calculated in this study to yield these sensitivity analyses. A summary of substitutions is shown in Table S below.

Table S: Summary of Sensitivity Analysis Outcome Substitutions

	6 Month Viral Load suppression percentage		12 Month Viral Load suppression percentage		18 Month Viral Load suppression percentage	
	Patients on					
	D4T/AZT	TDF	D4T/AZT	TDF	D4T/AZT	TDF
Study 903	NA	NA	84.1%	79.9%	71.1%	75.6%
Study 934	NA	NA	73%	84%	NA	NA

For sensitivity analysis with data from Study 903, outcomes for Arm 1 were calculated by substituting the d4T outcomes from Study 903 for data from this study. As all patients in Arm 1 are on d4T, the percent virally suppressed would be 84.1%. Sensitivity analysis outcomes for Arm 2 were calculated in the same manner as in section 4.2, “Outcomes per Arm.” Patients that developed side effects would be switched to TDF and therefore have the outcome of TDF patients from Study 903. Patients that had not developed side effects would be on d4T or AZT and therefore would have the outcome of d4T patients from Study 903. Table T below shows the distribution of outcome data in calculating the final outcomes for sensitivity analysis of Arm 2.

Table T: Arm 2 Outcome Calculation with Study 903 Data

Arm 2 Outcome Summary				
Patient group	number of patients	6 month VL suppression (%)	12 month VL suppression (%)	18 month VL suppression (%)
no side effects	306	NA	84.1	71.1
side effects q1 and q2	50	NA	79.9	75.6
side effects q3 and q4	61	NA	84.1	75.6
side effects q5 and q6	23	NA	84.1	71.1
Total weighted outcome		**NA**	**83.6**	**72.2**

Sensitivity analysis with Study 903 data for Arm 3 was also calculated in the same manner as described in section 4.2, substituting the outcomes from Study 903 for the data from this study. Patients that are in the "predispose" cohort will be started on TDF and therefore will have data from the Study 903 TDF patient group. Patients in the "non predispose" cohort will be started on d4T or AZT and will have data from the Study 903 d4T patient group. Table U below illustrates the assigned and weighted outcomes for Arm 3.

Table U: Arm 3 Outcome Calculation with Study 903 Data

Arm 3 Outcome Summary				
patient group	number of patients	6 month VL suppression (%)	12 month VL suppression (%)	18 month VL suppression (%)
predispose	363	NA	79.9	75.6
non predispose	77	NA	84.1	71.1
total weighted outcome		**NA**	**80.6**	**74.8**

Study 934 data were substituted in the same manner described above in order to calculate sensitivity analysis outcomes. Tables V and W below illustrate the outcomes calculated for Arm 2 and 3.

Table V: Arm 2 Outcome Calculation with Study 934 Data

Arm 2 Outcome Summary				
Patient group	number of patients	6 month VL suppression (%)	12 month VL suppression (%)	18 month VL suppression (%)
no side effects	306	NA	73	NA
side effects q1 and q2	50	NA	84	NA
side effects q3 and q4	61	NA	73	NA
side effects q5 and q6	23	NA	73	NA
Total weighted outcome		**NA**	**74**	**NA**

Table W: Arm 3 Outcome Calculation with Study 934 Data

Arm 3 Outcome Summary				
patient group	number of patients	6 month VL suppression (%)	12 month VL suppression (%)	18 month VL suppression (%)
predispose	363	NA	84	NA
non predispose	77	NA	73	NA
total weighted outcome		**NA**	**82**	**NA**

Tables X and Y summarize the sensitivity analysis outcomes for all arms. As rates of viral suppression were taken from the literature, the outcomes in the sensitivity analysis are different. At 12 months, d4T had a greater number of patients with viral load below 400 copies per millilitre. This results in a poorer outcome for patients on TDF in this sensitivity analysis. The outcome of each arm decreases in proportion to the increase in patients on TDF as seen in Table X. In contrast, in comparison to AZT, TDF has been shown to have greater efficacy. This results in a higher viral load suppression rate for patients that would be on a TDF regimen as seen in Table Y. As arm 3 has the greatest number of patients on TDF, the outcome for that arm is highest.

Table X: Sensitivity Analysis Outcome Summary (Using data from Study 903)

Option	6 Month VL Suppression (%)	12 Month VL Suppression (%)	18 Month VL Suppression (%)
Arm 1	NA	84.1	71.1
Arm 2 (TDF upon SE)	NA	83.6	72.2
Arm 3 (TDF for all predisposing)	NA	80.6	74.8

Table Y: Sensitivity Analysis Outcome Summary (Using data from Study 934)

Option	6 Month VL Suppression (%)	12 Month VL suppression (%)	18 Month VL Suppression (%)
Arm 1	NA	73	NA
Arm 2 (TDF upon SE)	NA	74	NA
Arm 3 (TDF for all predisposing)	NA	82	NA

The sensitivity analyses result in adjusted ICERs for each of the treatment arms. These ICERS are indicated in Table Z. Using data from Study 903, both arms 2 and 3 have better outcomes at 18 months than the status quo. This yields ICERS of R114.26 per percent of patients virally suppressed gained in 18 months on arm 2 and R456.77 per percent viral load suppression gained on arm 3 over arm 2. In other words, in a cohort of 100 patients, for each additional patient virally suppressed, it would costs R114.26 on arm 2 over arm 1 and R456.77 on arm 3 over arm 2.

Table Z: Sensitivity Analysis ICERs with Study 903 data

First line ART regimen alternatives	Cost of programme		
	Cost per patient (Rands)	Percent with undetectable viral load at 18 months	Rands/percent undetectable viral load gained
Status quo (arm 1)	8857.47	71.1	
Change to TDF upon development of side effect requiring change (arm 2)	8983.16	72.2	R114.26 per percent undetectable viral load gained over arm 1
TDF start for all with predisposing factors (arm 3)	10175.34	74.81	R456.77 per percent undetectable viral load gained over arm 2

As Study 934 does not have 18 month viral load data, the ICER needs to be calculated with outcome data at the 12 month interval (costs remain over 18 months). This also results in both arm 2 and 3 having better outcomes at 12 months than the status quo. The ICERs at 12 months are R96.68 per percent of patients virally suppressed gained on arm 2 and R153.24 per percent viral load suppression gained on arm 3 over arm 2. The results of sensitivity analysis are presented in the Table AA below.

Table AA: Sensitivity Analysis ICERs with Study 934 data

First line ART regimen alternatives	Cost of programme		
	Cost per patient (Rands)	Percent with undetectable viral load at 12 months	Rands/percent undetectable viral load
Status quo (arm 1)	8857.47	73	
Change to TDF upon development of side effect requiring change (arm 2)	8983.16	74.3	R96.68 per percent viral load gained over arm 1
TDF start for all with predisposing factors (arm 3)	10175.34	82.08	R153.24 per percent viral load gained over arm 2

Chapter 5: Discussion

1. Introduction

Resource poor, high HIV burden countries, are unlikely to have the human, infrastructural, or financial resources to treat all HIV positive individuals who are in need of ART. It is therefore necessary to consider how to ration treatment for as long as demand exceeds supply (Rosen, et al., 2005). Questions of distributive justice and how effective equitable ART care can be best delivered must be considered (Capron and Reis 2005; Egger, et al., 2005).

While the developed world has access to numerous drugs, sophisticated laboratory tools, and greater financial resources, treatment models for the developing world need to rely on simplification and decentralization of treatment. One component of simplification is the choice of drug regimen. The provision of a fixed-dose combination will facilitate adherence, optimising the chances of long-term success for ART. In addition, it will ease the pressure on supply chain management (Calmy, et al., 2004).

One choice for the simplification of ART regimen is the switch to a TDF based regimen. However, this switch involves increased expenditure on ART that is only partially offset by decreased management expenses. Unless the budget can be increased, the greater costs of TDF regimens would equate to a less equitable HIV programme as fewer people would have access to ART.

The benefits of TDF regimens to the patient include decreased pill burden and fewer side effects. Patients in settings where resources are not as limited have elected to access TDF for these benefits. The simplification of patient and health system management with a switch to TDF is also a significant consideration. For these reasons, information reflecting on the cost-effectiveness and cost- neutral status of a TDF first line regimen are necessary. If more beneficial health initiatives can be introduced without compromising the equity of the health system, steps should be taken towards implementation.

This thesis has indicated that significant financial resources would need to be invested in order to implement a TDF based first line regimen in South Africa. If 500,000 new patients are in need of ART every year, implementing arm 2 would cost R62,845,000 more than the status quo. This would result in a 1% increase in

expenditure. If arm 3 were to be implemented, it would cost R658,935,000 more than the status quo or an increase of 15% in expenditure.

In addition, with available outcome data, the benefits in terms of viral load suppression are not significant. However, quality of life and survival have not been considered in the outcomes. These would offer a more complete picture of the impact of TDF on the patient. The decrease in price of TDF to reach cost-neutrality in one intervention arm is not large. Sensitivity analysis with viral load outcome data from studies in the developed world has yielded ICERs that could help to advise on future implementation. The generalizability of this thesis to broader settings and the implications are discussed below.

2. Generalizability

GF Jooste hospital is an urban secondary level facility in the Western Cape. The resource limitations and conditions of rural facilities and health systems of other provinces may result in a difference in patient management capabilities, costs and outcomes.

2.1 Utilization of the health care system

The ARV Treatment Protocol for the Western Cape states that patients should be monitored by a medical officer at 4, 8, and 12 weeks on treatment. Thereafter, patients should be seen 3-monthly by medical officers and monthly by nurses (Provincial Administration Western Cape, 2004). In comparison, utilization data from this study indicates that patients averaged 5.5 appointments in the first 3 months and had appointments slightly more frequently than once monthly after the initial 3 months on ART (1.1 appointments per month). All appointments involved medical officer consultations. The greater utilization in this patient group leads to higher costs for general HIV management. This would decrease the impact that side effect management, with increased utilization, would have on the overall cost.

2.2 Rate of retention in care

A review of studies in sub-Saharan Africa concluded that African ART programmes are retaining approximately 60% of their patients in the first two years of ART care. Patients transferred to another ART site were considered to remain in care. There was significant heterogeneity between the studies with the spectrum ranging from 50% to 90% retention. Low median starting CD4 counts are prevalent

across the studies and impact on the survival rate of patients (Rosen, et al., 2007). In comparison, the cohort of patients in this study had a retention rate of 85% (374/440) at 18 months.

2.3 Viral load suppression rates

In a study of ART patients predominately residing in Cape Town's urban township areas, 70.9% of on-treatment patients had HIV viral load levels below 400 copies/ml at 12 months on ART (Orrell, et al., 2003). A study of patients in Khayelitsha township had a viral load suppression rate of 75% at 18 months on treatment (Coetzee, et al., 2004). While the study in Khayelitsha looked at patients in a public primary care setting, both studies were conducted on health services provided by NGO assisted programmes. A third donor funded ART programme in rural South Africa had 83% of its on treatment patients with viral load lower than 400 copies/ml at 12 months (Barth, et al., 2008). This study had 86.3% of those with viral load tests virally suppressed at 18 months on ART. The higher rate of viral suppression in the Jooste cohort could be explained by the presence of the IDR clinic, better monitoring of side effects, and lengthier and more thorough visits.

3. Strengths and weaknesses/limitations

In contrast to most cost analyses in South Africa, this study includes both outpatient and inpatient costs. In addition to primary and secondary ward costs, secondary referral costs are also included. Human resource costs comprise a significant portion of the secondary inpatient and referral service costs and result in significantly more expensive management. As human resource constraints are one of the major restrictions in the public health system, a costing that reflects components of patient management at all levels is important for appropriate policy decisions. In addition to improved outcomes, interventions should be considered in relation to the effective use of other scarce resources. If TDF can reduce the need for clinical services, it may be a reasonable intervention to implement.

In addition to representing 2 levels of patient care, GF Jooste Hospital is a standard public sector urban facility. The resources and constraints that affect GF Jooste are valid for public facilities across South Africa. While the IDR is unique to the hospital, it maintains a cost lower than that of inpatient care. If it is to be assumed that all patients referred to the IDR would otherwise require inpatient

stays, the cost of side effect management would increase. The costing with the IDR could be seen as a best case scenario.

As patient data were only available in paper form, a considerable amount of time was spent on data collection. Numerous data points were extracted from every patient visit. In order to collect data on inpatient stays, hospital folders were located and reviewed. These data allow for the inclusion of primary and secondary costs as well as all recorded laboratory investigations.

Limitations in data availability on TDF interventions in the developing world results in a number of assumptions for incidence of side effects as well as outcomes. However, due to the extensive data collection, the assumptions were kept to the lowest level possible. Secondary data from the literature have been used primarily in sensitivity analysis on patient outcomes.

Due to the high cost of TDF regimens, this study has looked at alternatives to the implementation of TDF as the full first line regimen. It has instead investigated options that may best benefit patients and the health care system by targeting those in most need for TDF. By suggesting alternative means of implementing TDF, this study provides information on the cost-effectiveness of practical means of implementation of TDF while minimizing inequity.

During the period from which this study drew its patients, a prospective trial of an adherence support model was in operation at GF Jooste Hospital. The trial, the DOT-HAART study, involved volunteer treatment supporters that provided direct observational support for ART patients. It is possible that increased monitoring and selection biases were introduced through this trial and that the patient group does not reflect the standard public sector primary care patient cohort. The majority of the patients in this study were in the DOT-HAART cohort. However, this study looks at cohorts within the group in comparison to each other. Therefore, the difference in outcomes between groups is not affected.

In addition, GF Jooste is a secondary care facility. The primary level infectious diseases clinic was initiated in order to fulfil a need when primary level facilities were not available in the area. The patient group has a larger geographic range than would be present in most primary clinics. The patients may also have had clinical or other differences from average primary sector patients.

As the primary level clinic is situated within the same facilities as the secondary level IDR clinic, it was difficult to distinguish between ID and IDR clinics

in hospital notes. Because of this, only visits that resulted in inpatient admissions were allocated to IDR appointments. This has lead to underestimation of IDR appointments and therefore a lower cost involved with complications on ART.

Without access to computer based patient data and with limited time, the sample size of the study (440 patients) is small. This has led to large confidence intervals.

Patient information was captured from patients initiating ART between December 2003 and June 2006. Most of these patients completed 18 months of ART before the decision was made to reduce the recommended dosage of d4T. This reduction in dosage and increased awareness of early symptoms for lactic acidosis has reduced rates of hyperlactataemia and lactic acidosis. This reduction would reduce the prevalence of d4T related side effects and therefore reduce the costs associated with management of d4T side effects.

Data for this study was taken from existing clinical notes. No quality of life outcome data are available for the patient group. This limited outcome calculation to viral load suppression which, while a good indicator of clinical improvement on ART, does not reflect many of the patient level concerns and a broader outcome.

Because of the higher costs associated with TDF based regimens and the limited resources in developing countries, long term studies of TDF in developing countries are not available. The utilization data was therefore limited to the substitution of data from the 'remainder' cohort for patients once they would be on TDF. Outcome data was limited in a similar manner. In sensitivity analysis, data on outcomes on TDF in comparison to d4T and AZT were sourced from studies in the developed world. Patient level and health system constraints in the developing world could effect the utilization and outcome results for TDF in these settings.

As this study took a health system perspective, costs associated with a societal perspective have been excluded. These costs include the added costs of d4T or AZT regimens over TDF regimens on the patient, family, and society. Discomfort from side effects could lead to lower productivity in the home and workplace. More frequent medical appointments would lead to greater travelling expenses and time off from work or family obligations for the patient and perhaps a supporter. Death of the patient due to side effects could reduce household income in the case of an employed patient. It could also lead to weakened family ties and a loss of parental or adult guidance.

While this study based utilization of health services for patients on TDF on a 'remainder' cohort of patients and used viral load suppression as an outcome, a recent study modelled utilization of health services, rates of side effects, and QALYs gained on TDF in a South African setting (Rosen, et al., 2008). The study addressed the cost and cost-effectiveness of switching from a d4T based first line regimen to a TDF regimen for all patients starting on ART. Data from published reports and clinicians' experience were used to estimate parameters for TDF utilization. The allocation of weights and duration for loss of QALYs per event were assigned from literature or estimated by clinical experience. Using these data, patients on TDF regimens had fewer events requiring change of regimen, and far fewer QALYs lost in comparison to the d4T patients. Despite the discrepancy in side effects and drug changes between the TDF and d4T groups, the high cost of TDF offsets added clinical and management costs. However, due to the benefits of TDF, a TDF first line regimen would be cost-effective at a price slightly lower than the current price. However in this case cost-effectiveness was based on a comparing the ICER to the GDP per capita which can be disputed. It would take a significant decrease in cost in order to make a full TDF first line regimen cost-neutral.

The alternative methods for determining costs and outcome in the above study and the results they yield, in combination with the alternative TDF implementation models discussed in this GF Jooste Hospital study, motivate for further research as to how TDF could be integrated into the South African first line ART regimen in a cost effective, equitable manner.

Chapter 6: Conclusion and Policy Implications

This study has shown that two options for the implementation of TDF as a first line ART lead to higher costs than currently incurred under the status quo. Data from the GF Jooste patient group has indicated that the higher costs associated with TDF would not result in significantly improved outcomes if this is measured narrowly as percent virally suppressed at 18 months. However, other benefits of TDF such as decreased frequency of side effects, lower pill burden, and ease of health management should not be discounted when making this decision.

Sensitivity analysis with outcome data from the developed world yields ICERs of R114.26 and R96.68 per percentage of patients virally suppressed over 18 months for arm 2 over the status quo. The data results in ICERs of R456.77 and R153.24 per percent of patients virally suppressed over 18 months for arm 3 over arm 2.

Threshold analysis indicates that a reduction to 83.5% of the current TDF price would make arm 2 cost neutral. While the outcome of increased viral suppression is not significantly different in the GF Jooste cohort or in published comparisons to d4T (Gallant, et al., 2004), these outcomes do not capture the broader patient based concerns that QALYs would. In addition, the societal costs associated with side effects from d4T and AZT have not been included. The potential added costs and benefits, some of which are indicated in a recent study (Rosen, et al., 2008), of a TDF regimen warrant investigation. If TDF were to be introduced as a first line regimen, the most cost effective option would be to change patients to TDF once they develop side effects.

If budgets cannot be increased, implementing a TDF based first line ART regimen would imply less access to HIV care for those in need while having little or no improvement in viralogical outcomes for patients. Morbidity and mortality including quality of life improvements and the positive impact that they may have on adherence and treatment success have not been reflected in this study. While TDF should not be introduced into first line ART at present, there are reasons to consider its future inclusion. As TDF reduces the burden on patient management, doctors' and nurses' time can be allocated to increasing the number of patients on ART. As human resources are likely the critical constraint in the public health care system, an intervention that leads to a better use of the available resources could be welcome, despite the added costs of the ART.

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Appendix 1

Utilization of health resources by cohort (cost per patient in SA Rands Sept 2008)

Utilization summary	Total	No Side Effect	Side Effect	No Predisposing	Predisposing	Remainder
Quarter 1						
ID appointment	1098.92	1067.01	1192.80	1125.36	1093.31	1130.49
IDR appointment	243.95	192.28	278.88	361.41	219.04	65.17
Ward day	19.58	28.16	73.49	0.00	23.74	0.00
ART regimen	457.30	469.49	460.46	495.32	464.94	494.23
Laboratory Investigations	303.28	297.57	316.31	312.84	301.25	277.68
Total quarter 1	2123.03	2054.52	2321.93	2294.92	2102.28	1967.58
Quarter 2						
ID appointment	601.13	586.40	637.66	591.49	603.15	572.80
IDR appointment	87.90	81.32	71.20	0.00	106.34	0.00
Ward day	6.19	27.98	18.37	0.00	7.48	0.00
ART regimen	466.44	511.55	463.77	477.73	489.82	478.50
Laboratory Investigations	382.36	376.19	394.51	341.95	390.84	336.92
Total quarter 2	1544.02	1583.43	1585.52	1411.17	1597.62	1388.23
Quarter 3						
ID appointment	510.87	499.89	532.10	532.19	507.95	529.69
IDR appointment	18.35	27.84	0.00	11.69	19.82	15.29
Ward day	6.31	9.58	0.00	0.00	7.67	0.00
ART regimen	459.69	486.56	414.26	473.32	471.34	477.79
Laboratory Investigations	100.28	92.70	114.93	99.97	100.66	81.14
Total quarter 3	1095.51	1116.58	1061.29	1117.18	1107.43	1103.91
Quarter 4						
ID appointment	571.30	516.19	683.27	498.12	586.71	484.89
IDR appointment	47.50	28.40	53.80	94.94	37.51	62.36

Ward day	28.78	9.77	18.51	165.35	0.00	0.00
ART regimen	488.36	512.39	442.83	472.69	491.66	482.17
Laboratory Investigations	348.12	298.24	442.64	296.52	358.99	274.76
Total quarter 4	1484.05	1364.98	1641.05	1527.63	1474.87	1304.18
Quarter 5						
ID appointment	516.06	457.76	622.95	536.13	511.76	514.69
IDR appointment	27.64	19.71	42.16	0.00	33.56	0.00
Ward day	6.58	5.09	18.65	0.00	7.99	0.00
ART regimen	533.55	539.52	522.63	527.52	534.85	506.50
Laboratory Investigations	170.25	123.78	256.44	118.39	181.37	96.87
Total quarter 5	1254.09	1145.86	1462.83	1182.04	1269.53	1118.06
Quarter 6						
ID appointment	479.05	442.81	547.04	463.96	482.26	426.23
IDR appointment	8.57	13.14	0.00	48.93	0.00	63.61
Ward day	3.32	5.09	0.00	18.94	0.00	24.62
ART regimen	548.06	544.14	564.56	525.69	556.67	506.50
Laboratory Investigations	317.77	279.38	380.42	309.97	319.43	298.97
Total quarter 6	1356.77	1284.56	1492.03	1367.49	1358.35	1319.93
18 month total	**8857.47**	**8549.92**	**9564.66**	**8900.43**	**8910.10**	**8201.89**