DESCRIPTIVE STUDY OF SURROGATE AND CLINICAL OUTCOMES OF ANTI-RETROVIRAL TREATMENT IN SELEBI PHIKWE, BOTSWANA FROM JUNE 2004 TO JUNE 2005.

George Sinyangwe

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Public Health

Selebi Phikwe, Botswana, 2010

Dedication

The completion of this work has taken close to five years. The process was slow and painstaking. I acknowledge the encouragement provided by my supervisor, Francis Akpan, who continued to keep me afloat when I was looking like quitting the process. This work is dedicated to my dear bother **Clement Sinyangwe,** who died from AIDS in the pre-antiretroviral therapy era.

Acknowledgements

The completion of this work has been a long walk for me and everybody involved. It has particularly been tough because I have to change towns, jobs, and countries in the course of doing this work.

I have several times felt like quitting. This painstaking work would not have stood chance of being completed without the support of my supervisor, Francis Akpan. My supervisor kept on resurrecting my hopes on many occasions when the mission appeared impossible. I would also wish to acknowledge the tones of encouragement that I received from Dr. Mary Kawonga of the School of Public Health, in the Witwatersrand University. Other acknowledgements go to the Ministry of Health of Botswana for allowing me to use their facilities and records.

George Sinyangwe, 2010, Lusaka, Zambia

Declaration

I, George Sinyangwe declare that this thesis is my own work. It is being submitted for the degree of Master of Public Health in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or other university.

.....

6th Day of April, 2010.

List of Contents

List of Tables

Appendix:

1. Adherence: Taking treatment according to prescriber's instructions
2. AIDS: Acquired Immune –deficiency Syndrome.
3. ARV: Anti-retroviral drugs
4. ART: Antiretroviral therapy
5. CD4 cells: These are specialized white cells and are involved with other cells in immune responses. It is this cell that is usually depleted in later stages of HIV infection to lead to immune suppression.
6. Cross-sectional Study: In this study design, exposure and outcomes observed and measured at the same time
7. HIV: Human Immune-deficiency Virus.
8. Nevirapine: It is a non-Nucleoside Reverse Transcriptase ARV drug
9. Prevalence: Number of people with the infection, compared to people at risk
10. RCTs: Randomized Controlled Trials
11. RNA: Ribose Nucleic Acid
12. Treatment naïve: Patients who have never received ARV treatment
13. UNAIDS: United Nations AIDS
14. WHO: World Health Organization
15. Viral Load: Number of HIV copies in a milliliter of blood.

Background

Few results are available concerning long-term clinical outcomes in ART treatment programs. The objective of this study was to describe clinical and laboratory outcomes for adult patients commenced on ART in Selebi Phikwe, Botswana from June 2004 to June 2005 within one year of commencement of ART.

Methods

Cross-sectional descriptive study of clinical and laboratory outcomes for 904 adult patients initiated on ART in Selebi Phikwe, Botswana, from June 2004 to June 2005. Data from ART services statistics was analyzed using descriptive statistical methods.

Results

Most patients had low a basal CD4 cellular count with a median count of 25 cells, which rose to 147 after 12 months of treatment. Of the 84 (9%) deaths, 75 (89%) had a basal CD4 count of less than 10 cells and 48 (57%) died within three months of commencing of ART

Conclusion

Good clinical and laboratory outcomes for patients on ART in resource limited are achievable. Mortality commonly occurs among patients with low CD4 counts and within three months of commencement of therapy.

CHAPTER I: INTRODUCTION

1. 1 Background

Sub-Saharan Africa remains the most affected by the AIDS pandemic, with more than two thirds (68%) of all people infected living there (UNAIDS, 2008). Estimates show that one in every five adults in the region is infected with HIV, and that patients with HIV-related illnesses occupy up to 70% of hospital beds (Ahn, M. J., Grimwood, G., Schwarzwald and Herman, 2003).

Sub-Saharan Africa is also besieged with a devastating strain of HIV (HIV-1C), a sub type that is more virulent, and displays greater degree of mutation compared to the HIV strains found in United States of America and Europe (Ahn, et al., 2003).

Botswana, like the rest of sub-Saharan Africa, has not escaped the pandemic. The prevalence of HIV in the general population is 17.1% (Botswana AIDS Impact Survey II, 2004). It is further estimated that 33.4% of the sub-population in the 15-49 year age group is HIV positive (Botswana HIV/AIDS second-generation surveillance, 2005).

Faced with the burden of HIV, the Government of Botswana engaged the services of McKinsey & Company, an international management firm with expertise in strategy, to determine the feasibility of a country-wide provision of free antiretroviral therapy (ART).

In 2001, the consultancy concluded that 33.3% of the 300,000 HIV-infected people in Botswana were in urgent need of antiretroviral therapy (ART Project description document, Government of Botswana, 2002).

A constellation of the fore-going scary statistics, the impact of HIV/AIDS on the quality and length of life, and the strong political commitment of President Festus Mogae, led to the introduction a public sector ART program in Botswana in January of 2002.

Botswana has now completely implemented the free ART program across the entire country, having started with four pilot sites in 2002 (Ministry of Health of Botswana, 2005).

It is against this background that a study to describe clinical and laboratory outcomes within one year of commencement of ART for adult patients started on ART between June 2004 and June 2005 in Selebi Phikwe, Botswana is proposed.

1.2 Problem Statement and Justification

At the time Botswana embarked on a nation-wide public sector ART program, there were no relevant international comparisons nor up to date data and/or contextually appropriate operational or clinical research and information to inform the program (ARV project description document, Government of Botswana, 2002). Following the example of Botswana, public sector ART programs are now being implemented in most sub-Saharan countries (Bussmann, H., et al., 2008), and despite logistical hurdles, the number of individuals able to access ART in the region has increased (Lawn, Myer, Bekker, and Wood, 2006).

To date, few results are available concerning clinical outcomes in treatment programs (Bussmann, H., et al., 2008). Further, the few available studies devoted to measuring outcomes only speak to a limited range of outcome variables. For example, a recent longitudinal study of 153 ART naïve patients initiated on treatment at the Gaborone/Botswana site was only concerned with virologic and immunological outcomes, and demonstrated viral depression to <400 copies/ml in 87% of the patients and a mean rise in CD4s count of 149/ml in 24 weeks (Wester, C. W., et al., 2005)

Most recent information about outcome variables has come from randomized controlled trials (RCTs). However, RCTs have their own limitations which include: limited numbers of experimental subjects, huge costs, and the tendency by researchers to place emphasis on surrogate outcomes such as early laboratory makers rather than on long term clinical end points (Sabin, A.C. and Philips, 2001).

Descriptive studies of outcomes in patients on ART in non experimental settings (natural settings) in the sub-region may provide accurate information on the following aspects: 1) the actual outcomes (surrogate and clinical) in a natural rather than experimental setting; 2) the factors that influence outcomes, and 3) how well ART outcomes in Botswana compare with other countries and regions.

Information from such studies has potential to inform ART-related policy in Botswana and many other countries with similar context. Travis, et al., (2004) argue that politicians and policy makers, in general, take heed of research conclusions in arriving at policy. Descriptive studies of outcomes on ART might help to inform ART-related policies in countries where political commitment to ART might be weak.

The falling prices of ART, the advent of generic ART, and the pressure on the rich north to put more resources into the fight against HIV have led to a plethora of ART activities in the sub-Saharan region. Therefore, natural setting experiences with ART could be important in 1) informing future ART policies in the region, 2) contributing to changing HIV-related health seeking behaviors among communities, and 3) contributing to improved management of HIV in public hospitals.

It is with this background that this cross-sectional descriptive study to describe clinical and laboratory outcomes in adult patients initiated on ART in Selebi Phikwe, Botswana from June, 2004 to June, 2005, has been proposed. This cross-sectional study will be a valuable contribution to the existing literature describing the experience of clinical and laboratory outcomes in individuals initiated on ART in Botswana and sub-Saharan Africa. Unlike Randomized Controlled Trials, in which the participants might be 'motivated' and thus, more adherent to therapy (Sabin and Philips, 2001), the experience in Botswana should reflect a routine clinical environment, and not an experimental one.

1.3 Research question

What are the clinical outcomes experienced by patients within 12 months of initiation of ART in resource-limited settings like Botswana?

1. 4 Literature review

1.4.1 Trials aimed at safety and efficacy of anti HIV drugs: The observation of the first cases of the newly acquired immunodeficiency syndrome (AIDS) back in 1981 subsequently led to an unfortunate spread of the disease and a rising death toll. Along with the sharp rise in HIV-related morbidity and mortality, public awareness of urgent need for effective antiretroviral (ARV) therapy rose (Emmelkemp and Rockstroh, 2007). Phase II clinical trials were to play an important role in helping to understand the efficacy and safety of the early ARV drugs. In 1987, a double-blind placebo-controlled trial including 282 patients with AIDS was performed. The efficacy of oral AZT 250mg every four hours was evaluated and compared with placebo. After 24 weeks, treatment with AZT was associated with lower occurrence of opportunistic infections, significantly lower mortality, and a higher increase in CD4 count compared with placebo (Emmelkemp and Rockstroh, 2007). However, there are numerous dissident views that phase II trials for early ARV drugs may have been rushed because of the urgency to stem the AIDS mortality.

1.4.2 Monotherapy: The first ARV substance to become available was Zudovudine (AZT) (Emmelkemp and Rockstroh, 2007) and the first available agents to treat HIV infection were nucleoside reverse transcriptase inhibitors such as Zidovudine (AZT), lamivudine (3TC), and didanosine (ddl) (Youle and Wainberg, 2003). However, after initial promising results of short-course treatment with first nucleoside reverse transcriptase inhibitors (NRTIs), disappointment was great when studies with longer follow-up showed no superiority in disease progression and survival (Emmelkemp and Rockstroh, 2007). The Concorde study in 1994 showed that after a median follow-up of 3.3 years there was no statically significant difference in clinical outcome between patients treated immediately at randomization with AZT 250mg every four hours and those receiving placebo or deferred ARV treatment in case of advanced disease. Several trials further indicated that early initiation on AZT monotherapy in asymptotic HIV-infected patients was not beneficial (Emmelkamp and Rockstroh, 2007).

1.4.3 Combination therapy/Highly Active Antiretroviral Therapy (HAART): Because the benefits of monotherapy with AZT had been shown to be only transient or insignificant, there was strong need for the development of new ARV therapy and strategies. In this context, new trials were initiated to evaluate the efficacy of ARV combination therapy. In 1995, the Delta trial compared AZT monotherapy with a combination of AZT with didanosine (ddl) or Zalcitabine (ddl). This large international trial included 3,207 patients and reported a significant difference in survival between the treatment groups (Emmelkemp and Rockstroh, 2007). A Glaxo-Wellcome sponsored study has demonstrated that the addition of lamivudine (3TC) to ATZ monotherapy improved clinical outcomes, at least in the short term (Gazzard, 2001). Further studies have demonstrated that protease inhibitors contained in triple therapy combinations delayed clinical events, as compared with dual nucleoside regimes (AZT/3TC), in a group of patients with advanced disease who had at least three months of previous AZT monotherapy experience. A systematic review, meta analysis and meta-regression of 54 fully reported randomized trials has also shown that triple therapy has significantly improved clinical and surrogate outcomes compared with dual therapy (Jordan, Gold, Cummins and Hyde, 2003). Since the major biological factor in failure of antiretroviral therapy is the development of viral mutations which confer resistance to specific antiretroviral agents, a two drug regimen has a more durable effect than a single drug regimen, simply because more viral mutations are required to confer resistance to two antiretroviral drugs. Similarly, resistance to a potent three drug regimen generally takes longer to develop than to a two drug regimen (Carpenter, 2002).

1.4.4 Why descriptive study: The major weakness of most data on outcomes of ART is its source, randomized controlled trials (RTCs). Most up to date information on outcome variables for individuals treated with ART comes from randomized controlled trials. Data on individual patients would allow better exploration of the effects on individual patient characteristics (Jordan, et al., 2003), and descriptive studies which follow up patients in their treatment centers and use routinely collected data will be complimentary to randomized controlled trials (Sabin and Phillips, 2001).

1.4.5 Provisos for a successful ART program: The provisos for a successful ART program differ from those of other disease programs in a lot of ways because 1) most ART treatment programs usually have a backlog of patients in immediate need of treatment at the same time, 2) despite having the highest burden of HIV, sub-Saharan Africa does not have adequate numbers of HIV practitioners to treat HIV-infected patients, and 3) infrastructure and equipment required for treating HIV is often inadequate. A good HIV program should provide standardized and affordable and/or free HIV treatment, standardized monitoring systems, uninterrupted drug supply, decentralized ART clinics to improve physical access, community involvement, and use of ART services to deliver other services such as family planning. In a review of ART programs conducted by Akileswaran and others, the program that accounted for the highest mortality rate of 27% required its patients to pay for medication, and other authors admitted that safety and efficacy became compromised as a result (Akileswaran, 2005). Stringer and others (2006) report that the Zambian ART program scored early successes because of leadership and advocacy by the Zambian government, task-shifting to address physician shortage, funding from PEPFAR and the Global Fund, and a sound information system.

1.4.6 When to initiate ART: Doctors are learning more about the best way to treat HIV, but it is still not known for certain when is the best time to start taking anti-HIV treatment (Aids map, 2008). In arguing against CD4 count of less than 200 cells per milliliter of serum as the gold standard for initiation of ART, Wood (2005) has calculated that in absence of ART, an infected adult dies in six years, and his life expectancy goes up by 17 if started on ART at CD4 < 200. However, when ART is started at CD4 > 200 the life expectancy is extended by 23 years. The down side of Wood's argument is that it is based on mathematical modeling with a lot of assumptions. Another study has demonstrated that long-term immune recovery is possible regardless of baseline CD4+ T-cell count. However, patients who start therapy with a CD4+ T-cell count >200 cells/mm3 have poorer immunologic outcome as measured by the proportion of patients with CD4+ T cells <200/mm3 or >500/mm3 at last determination (Garcia, 2004). Gazzard (2008) has

suggested that HIV infected patients should be initiated on treatment when their CD4 counts are > 350 cells/ml.

1.4.7 Late presentation and gender: Results on which gender presents late for diagnosis and treatment of HIV (CD4 counts below 50 cells per milliliter of blood) differ from country to country. A study to inform on clinical outcomes for late presenters (CD4s < 50/ml), observes that the late presenters are likely to be female and that mortality amongst late presenters is 13% (Sabin, et al., 2004). The strength of Sabin and others' findings are that the population of late presenters was large (110 (15.3% of the subjects started on ART) and the follow-up was long enough (up to two and half years). Another study, a cross-sectional survey conducted in Venezuela between May 2005 and October 2006 to determine the rate of late presentation and the gender that presents late involving 225 patients concluded that females rather than males were less likely to present late for care (Bonjour, et al., 2008).

1.4.8 Prognostic indicators: On early prognostic surrogate makers, Smith, et al., (2004) have shown that the viral loads at 4 weeks of treatment with ARV may predict the viral loads at 24 weeks in treatment naïve patients. Patients with viral loads < 50/ml at 4 weeks retained the status, while those with loads between 1 001-10 000/ml, were only able to reduce to < 50 in 64% of patients. The weakness of using viral loads as prognostic indicators for patients on ART in a public sector program in Africa is that not many countries will use serial viral load tests because prohibitive costs. Botswana for example, has stopped serial viral loads and CD4 assays to follow-up patients because of cost. Zambia does not even use viral loads in the routine management of HIV. In a retrospective study done in Cambodia on outcomes of highly active antiretroviral treatment (HAART), the study demonstrates that the factors associated with virologic failure at 24 months (viral loads greater than 1000 copies/ml) include previous ART exposure, age greater than 35 years, a low CD4 count (less than 200/ml), presence of an opportunistic infection at 9-24 months and a low plasma concentration of ART at 24 months (Ferradini, et al., (2008).

1.4.9 Outcomes (Definition): Treatment outcomes reported from various clinics in sub-Saharan Africa, Haiti, Asia and South America have been good, comparable with those observed in countries with higher incomes. Patient outcomes are usually categorized as patients alive and on treatment, stopped treatment, transferred to another facility, dead or "lost to follow-up" (Joseph Kwong-Leung Yu, et al.,2007**).** A South African study conducted at the Ndlovu Medical Center (NMC) categorized outcomes as 1) patient retention (proportion of patients remaining in care, combined with the proportion of patients who had been transferred to other clinics, 2) patient attrition (all-cause mortality plus loss to follow-up), 3) Virological suppression (achieving HIV-RNA below 50 copies/ml, and 4) immunological failure (failure to raise CD4 counts to more than 100 cells/ml (Barth, 2011).

1.4.10 Clinical Outcomes: Clinical outcomes for patients on ART in resource-limited countries are comparable to those of the first world. A search of academic databases and recent conference abstracts involving studies from 14 countries reported improved clinical outcomes in all the studies in terms of weight gain and reduced mortality (median mortality was 7%) (Akileswaran, 2005). However, methodological discrepancies between the African studies and those coming out of industrialized may also account for the inability to easily compare data. In a report by Stringer and others (2006) on the outcomes of 16,000 patients receiving ART from 18 public sector health facilities in Zambia between April 2004 and November 2005, a total of 1,142 (7%) patients receiving ART died and death occurred within the first 90 days on treatment; after 90 days, there were only 5 deaths per 100 patient-years, comparable to the rates in the first world; and 861 patients failed therapy (therapy failure defined as worsening stage of disease after three months of therapy or return of CD4 below pre-treatment levels. A retrospective analysis of a cohort of adults who initiated on treatment in five public sector sites in three African countries reported a mortality rate of 8 deaths per 100 person-years and mortality was highest in the thirst six months of treatment (Palombi, L., et al, 2008).

1.4.11 Laboratory Outcomes: A recent clinical trial on the effects of the current generation of ART drugs on viral loads has demonstrated a viral suppression to <50/ml in

70% of subjects (Havlir, 2004). Miller (2004) also observes that the current therapy for HIV-1 can achieve full suppression of HIV-1 RNA (<50 copies/ml). However, achieving a higher level of viral suppression does not always confer greater increase in CD4 counts, much against previous studies (Havlir, 2004). Another study which reviewed twenty-eight abstracts and articles involving 14 African countries on the feasibility of implementation of ART programs and clinical and laboratory outcomes has demonstrated an increase in the mean and median CD4 count, a median of 73% patients with undetectable viral loads, median weight gain of 5.0kg, and median mortality rate of 7.4% using a regimen of two nucleoside reverse transcriptase inhibitors (NRTI) and one non nucleoside reverse transcriptase inhibitor (NNRTI) (Akileswaran, et al., 2005). A 5.4 month follow-up of 709 on the national public ART program in Botswana to determine clinical and laboratory outcomes on ART showed that patients managed in a national ARV program in resource poor areas have clinical outcomes comparable with those in well-resourced areas even when they start treatment at relatively low CD4 counts (Naledi, N.T., et al., 2004). The weaknesses of this study that would limit its use in predicting ART outcomes of other national ARV programs in similar settings are the short period of follow-up and the relatively small numbers of experimental subjects. In South Africa, a follow-up of 287 treatment naïve adult patients in a community-based antiretroviral therapy (ART) **program established in 2001 in a South African township** has also demonstrated that ART can be provided in resource-limited settings with good patient retention and clinical outcomes(Coetzee, et al, 2004). The weakness of this study limiting its use in predicting outcomes in similar settings is the small number of experimental subjects. The South African study conducted at the Ndlovu Medical Center including 735 adults who started ART showed the following outcomes: 1) retention rate was 65%, 2) mortality was the main cause of attrition, 3) mortality typically occurred in the first three months of initiation of treatment, 4) viral repression in 76% of the patients, and 13% immunological failure (Barth, et al., 2011)

1.4.12 Adherence: Although there is no universally accepted definition of adherence, medication adherence may be defined as the extent to which a patient takes a medication in the way intended by a health care provider (Machtinger and Bangsberg, 2006).

Antiretroviral adherence is the second strongest predictor of progression to AIDS and death, after CD4 count (Machtinger and Bangsberg, 2006). Patients therefore need to adhere to treatment to ensure good clinical and laboratory outcomes. Adherence to ART is most impactful if it is observed from the beginning of treatment. Research has demonstrated that the initial response to ART has long-term prognostic significance, and optimizing adherence in early months is important for ensuring long-term immunological and virological success (Brinkholf, W. G., et al., 2009). Data on when (phase during treatment) non-adherence is most likely to occur in an ART program is mixed. Data from the ART-LINC collaboration and other treatment programs such as the Médecins Sans Frontières (MSF) program in Malawi show that loss to follow-up and death mostly occur in the first 6 months after ART initiation (Brinkholf, W. G., et al., 2009). Not all studies confirm this, however. Data from a South African ART programs demonstrate that while mortality decreased rapidly after ART initiation, the rate of loss to follow-up remained fairly constant during the first 2 years (Brinkholf, W. G., et al., 2009).

The level of adherence has significant impacts on clinical and laboratory outcomes for individuals taking ART. Studies have demonstrated that ART requires an adherence rate of more than 95% for good virologic and immunological response (ARV Project Description Document, Government of Botswana, 2002). Adherence to ART of more than 95% has been shown to suppress viral loads to less 400 copies/ml in 78% of patients; 90-95% adherence has resulted into similar viral decay in only 45% of patients; 80-90% adherence has suppressed viral loads in 33% of patients; 70-80% adherence has been shown to suppress viruses in only 29% of patients; and less than 70% adherence suppresses viruses in only 18% of patients (Bartlett and Gallant, 2004). A randomized controlled trial conducted between 1996 and 1998 to determine the association between adherence and virological response, has shown that patients exhibiting biological success had significantly greater adherence early in therapy compared with patients who failed, and that greater adherence was required for viral decay to less than 50 copies/ml than for 400 copies/ml (Rathbun and Farmer, 2002)

The performance of various ART programs in the area of adherence has been fairly mixed. Using data on the performance of different ART programs in resource-limited settings in relation to adherence, Brinkhof and others (2009) have found out that 21% of patients had been lost to follow-up by 15 programs within the first six months. Another study in an urban primary health care setting of Kamapala, Uganda, 3406 (21%) of 16 199 patients starting ART in 2004–2005 were more than 30 days late for a scheduled pharmacy appointment (Brinkholf, W. G., et al., 2009). A South African study at the Ndlovu Medical Center had an attrition rate of 35% (comprising actual loss to follow-up and patients who died while on treatment (Barth, 2011)

In a prospective study, 140 individuals in a public hospital HIV clinic were followed for one year after initiation of ART. The investigators assessed adherence using three methods: a computer chip embedded in a specially designed pill-bottle cap to record the time and duration of each bottle opening (microelectronic monitoring system (MEMS), or MEMS caps), pill count, and self-report. They calculated a composite adherence rate including all three measures that demonstrated a mean adherence rate of 71% (Machtinger and Bangsberg, 2006).

Studies show that loss to follow-up is mainly due to the large number of patients that programs have to follow-up in public programs. Brinkhof and others (2009) observe that treating the maximum number of new patients possible has been the top priority for many public sector programs, with the possible consequence that documenting and tracing patients lost to follow-up has become increasingly inadequate. Using data from a large collaborative network of ART treatment programs in resource-limited settings, Brinkhof and others (2009) also found out that the percentage of patients lost to programs was substantially greater in more recent calendar periods than in the period before the year 2000. This suggests that many sites find it increasingly difficult to follow-up the growing population of patients and to trace those not returning to the clinic ((Brinkholf, W.G., et al., 2009). Other documented reasons for loss to follow-up are drug abuse, low household economies, and old age. A study conducted to explain reasons for missed appointments has concluded that substance abuse is a leading cause of poor adherence and eventual loss to follow-up (Hewitt, et al., 2002). Oyugi and Bangsburg (2002) have

also argued through studies that household economies have an impact on the levels of adherence. Low household income limits access to health services, including ART services because the little income will be deviated to food and other needs and not health. In the Botswana program, adherence by individual patient's frequency of attended medical refill, while loss to follow-up was patients who could be traced for at least three months (Bussmann, 2008).

1.5 Aim

The aim of the study was to describe clinical and laboratory outcomes for adult patients commenced on ART in Selebi Phikwe, Botswana, from June 2004 to June 2005.

1.6 Study Objectives:

I. To describe the following clinical outcomes among adult patients initiated on ART in Selebi Phikwe, Botswana from June 2004 to June 2005 within 12 months of commencement of ART: 1) death outcome, 2) lost to follow up, and 3) length on treatment before death.

II. To describe the following laboratory parameters for ART-eligible adult patients started on ART in Selebi Phikwe, Botswana from June 2004 to June 2005: Basal CD4 characteristics (central tendencies and dispersions) and CD4 characteristics (central tendencies and dispersions) after 12 months of ART.

CHAPTER 2: Method and Materials

2.1 Introduction to Methods and Materials

This chapter describes the 1) study design, 2) study site and reasons for its selection, 3) study population, 4) sampling methods, 5) sources and methods of capturing, cleaning, and analyzing data, 7) quality of data, and 8) ethical considerations during the entire process.

2.2 Study design

This was a cross-sectional descriptive study of HIV-infected adult patients initiated on ART in Selebi Phikwe, Botswana, from June 2004 to June 2005 to describe 1) basal CD4 counts at the beginning of treatment, 2) CD4 counts at 12 months, 3) death and loss to follow-up outcomes during the first 12 months of treatment, 4) the basal CD4 counts profile for patients who died, and 5) the time on treatment for patients who died.

2.3 Brief Description of study site

2.3.1 Location: The setting was Selebi-Phikwe, a small mining town located in the north-eastern part of Botswana, with a surface area of 384 hectares. It lies within the Bobirwa sub-district whose headquarters is Bobonong, 80 km further east. Another secondary center, Mmadinare, lies 17 km north-west of Selebi Phikwe. Though the town only has a population of 60,000 people, it also serves people from nearby towns/centers because of its well developed infrastructure (District Health Annual Report, 2003).

2.3.2 Communication: The town is endowed with good road communication that links the town to the rest of the country and to the Limpopo province of the Republic of South Africa (District Health Annual Report, 2003).

2.3.3 Commercial activity: The main source of employment is the Bamangwato Concessions Limited (BCL) mine which excavates mixed copper-nickel ore from several shafts in deep and opencast mines.

.3.4 Demography	2004	2005	2006
1. Total Population	**57472**	**58851**	**60264**
2. Children	1286	1317	1348
3. Children 0-4 years	5605	5740	5877
4. Age 5-14	6788	6951	7118
5. Women 15-49	16853	17258	17672
6. Men 15-49	19729	20203	20688
7. Women 15-64	19450	19917	20395
8. Men 15-64	23229	23786	24357
9. Older than 64	1114	1140	1168
Number of expected deaths (from CDR)	315	324	329
Total number of notified deaths	457	600	539
Notified deaths as % of expected	145%	185%	164%

The Selebi Phikwe District Health Report of 2008

2.3.5 Burden of disease

The town has an adult HIV prevalence rate of about 46% (Botswana HIV/AIDS second-generation surveillance, 2005).

2.3.6 Health Services

Selebi Phikwe has one government hospital, one mine hospital, six council clinics, and seven private clinics. Accessibility to health facilities is within a radius of 8 km.

2.3.7 Selection of study site

The choice of Selebi Phikwe as the study site was determined by two factors: 1) the site was convenient because the principal investigator had worked in the town and had helped in setting up the ART program in the public sector, including development of program tools, protocols, and procedures and 2) the town had the highest prevalence of HIV in the country; therefore, there was high chance that more subjects would be evaluated during the period covered by my study compared to low HIV prevalence towns in Botswana.

2.3.8 Study population

All HIV-infected adult patients initiated on ART in Selebi Phikwe, Botswana, from June 2004 to June 2005 were included in this study (population size 904). The recommended first line treatment for patients initiated on ART in Selebi Phikwe, Botswana from June 2004 to June 2005 composed of Zidovudine (AZT), Lamivudine, and Niverapine or Efeverenz. The criteria for initiating patients on ART were based on CD4 counts being less than 200 cells per milliliter of blood and /or presence of an AIDS-defining illness (WHO classification).

2.3.9 Sampling not required; all patients enrolled on ART during this period were included

Sampling was not required for this study because it was apparent during the study design that the population of HIV-infected patients initiated on therapy would not be too large to require a representative sample to be drawn from the study population. It was feasible that all the patients screened for ART and started on ART would be included in the study. The population was 904 adults started on ART.

2.4 Sources of data

Each patient screened for ART and/or started on treatment had a patient file kept at the health facility. The file was updated each time the patient came for review and/or collected drugs. The file had personal information, the reason why a patient tested for HIV, the date on which ART was commenced, the ART regimen, pill count results laboratory test results, and review dates.

In addition to the ART file kept at the facility, each patient screened for ART and/or initiated on ART kept an out-patient card, which was updated at every patient visit. This was a simple tool bearing a patient's name, the ART regimen, and the review dates.

The pharmacy also maintained records of ART issued to patients, which were updated every time a patient collected or missed collection of ART. This record was both in hard

copy and electronic forms. It included the patient's personal information, the ART regimen, the ART refill dates, and records of missed appointments.

The laboratory also maintained hard copy records of laboratory investigations done and the results for patients screened for ART and/or already on ART.

At the time the time was being collected, Botswana was also trying to implement an electronic ART register called the integrated patient management system. The system was initially besieged with teething problems.

To access health records, the researcher must obtain permission to have access to patient files by getting ethical clearance from the Ministry of Health of Botswana and the Public Health Specialist for Selebi Phikwe and Bobirwa who is the principal custodian of health records

2.5 Data capture tool

A two paged (size A4) data collecting document with the following variables was designed:

1. Patient code
2. Age and Sex
3. Employment status (None, formally employed, self employed)
4. Level of education (None, primary, secondary, tertiary)
5. CD4 counts at 0, 3, 6 and 12 months.
6. Viral loads at 0, 3, 6 and 12 months.
7. Clinical outcomes

The data capture tool was piloted on 50 study subjects to validate its use on the entire study population. Generally, the data capture tool was discovered to be user-friendly. However, the pilot also revealed that certain data that we had hoped to collect could not

be collected because the district had stopped to collect these data routinely. These data included: 1) serial viral loads, 2) information on education status of patients, and 3) use of recreational drugs.

2.6 Type of data

The following data were collected: 1) baseline data on CD4 counts at the initiation of therapy and 2) CD4 counts at 12 months of ART, 3) death and loss to follow-up outcomes within the first 12 months of commencement of ART, 4) length on treatment before death, and 5) basal CD4 count profile for patients who died while on ART among adult patients started on ART in Selebi Phikwe, Botswana from June 2004 to June 2005. These data covered a period from June 2004 up to July 2006 to allow all the study subjects who had been initiated on ART from June 2004 to June 2005 to have gone through treatment for 12 months.

2.7 Reliability of data

The following standards were put in place to ensure that the data collected was correct and complete.

1. Data was extracted manually from patients' cards to the data collecting tool. In event of data gaps, other data sources such as pharmacy records and laboratory records were used.
2. The extraction of data was primarily done by the Principle Investigator.

2.8 Validity of data

Validity is an expression of the degree to which a test is capable of measuring what it intends to measure. The study should accurately describe 1) basal CD4 counts, 2) CD4 counts after 12 months of ART, death and loss to follow-up outcomes within the first 12 months of ART because of the following attributes:

I. Validity by virtue of study design: The study will describe outcomes in a non experimental setting (natural setting)

II. Validity by virtue of population selection: As indicated above, no sampling was done because it was feasible to include the entire population of adult patient s started on ART in Selebi Phikwe, Botswana, from June 2004 to June 2005 in the study.

2.9 Data cleaning

Data was imported onto an electronic excel spreadsheet for descriptive statistical analysis. For numerical data such as age (which were already represented by numbers), those numbers were used as codes. For non numerical variables such as gender/sex, codes were created for male and female. This was done during the extraction of data. After entering data on the spreadsheet, data was checked for entry errors (completeness and appropriateness) by using the sort function in excel, which made it easy to identify data gaps and entries that appeared inappropriate. Further data was checked for non numeric entries in columns and rows where they were not designated to be. Whenever a gap was identified, the paper-based records (patients' files) maintained in the health facilities were used to determine the reason/s and/or complete the gaps.

2.10 Data Analysis:

The descriptive statistics of interest in this study were the measurement1) of the central tendency of outcomes data using the mean, median and mode, 2) the dispersion of outcome data using frequency distribution tables, and calculation of ratios.

2.10.1 Age range with most patients on ART: A frequency table with 13 age intervals between the ages of zero and above 60 was created for the numbers of adult patients started on ART using excel statistical analysis toolpack. This was done to make it easy to understand the distribution (dispersion) of patients on ART according to age (

2.10.2 Basal CD4 counts: A frequency table with eight CD4 count intervals was created in excel to show the number of patients per CD4 frequency interval. This was done to show the (dispersion) distribution of patients started on ART per CD4 cell count band. Further, the central tendency of basal CD4 counts was measured using the excel data analysis toolpack. The variables of interest were the range, mean, and median basal CD4 counts.

2.10.3 CD4 counts after 12 months of treatment

A frequency table with eight CD4 count intervals was created in excel to show the number of patients per CD4 frequency interval after 12 months of treatment. This was done to show the (dispersion) distribution of patients per CD4 cell count band after 12 months on ART. Further, the central tendency of CD4 counts at 12 months was measured using the excel data analysis toolpack. The variables of interest were the range, mean, and median CD4 counts.

2.10.4 Death outcome: For the patients who died while on ART, the excel sort function was used to sort out the patients by dead or alive status and then by age, basal CD4 count, and length on ART before death. This data was then used to construct the following frequency tables: 1) the distribution of dead patients per age band, 2) the distribution of dead patients per basal CD4 cell count interval, and the distribution of dead patients according length on treatment before death.

2.10.5 Lost to follow-up: For patients lost to follow-up, the excel sort function was used to sort out patients lost to follow by age. A frequency chart was constructed to show the distribution of patients lost to follow-up by age interval.

2.11 Ethical considerations

The main ethical issue associated with this study was details about individual patients getting into wrong hands. When data was imported from patients' records maintained by health facilities, no names were imported (codes were used). Consent from individual patients was not deemed necessary by the ethics committee of the Ministry of Health of Botswana and the principal investigator because of 1) identifying names were not used and 2) the study did not in any involve interviews with and/or manipulation of human subjects. The study addressed other ethical requirements through observance of the following:

2.12 Ethical clearance

I. Clearance by the ethics committee of the University of Witwatersrand: The proposal was cleared by the ethics committee of the university.

II. Clearance by the ethics committee of the Ministry of Health of Botswana: The proposal was cleared by the ethics committee of the Ministry of Botswana. The ethics clearance from the Ministry of Health did not require individual consent because the study did not include interviews with patients and/or manipulation of human subjects. As a matter of fact, the ethics committee of the Ministry of Health of Botswana was provided some valuable input.

2.13 Confidentiality: The data imported from patients' did not have individual patient names. In addition, the principal investigator was the only individual responsible for importing data.

2.14 Beneficence: It was hoped that the results/findings of the study would have three potential benefits, namely:

I. The findings would add to biomedical knowledge on clinical and laboratory outcomes for patients started on ART in resource limited settings

II. The findings would stimulate further research on clinical and laboratory outcomes for people initiated on ART in resource settings

III. The findings would inform policy on ART in resource limited settings

2.15 No risk/Non malfeasances: The study did carry any risks of physical injury because the intervention did not involve interviews with the study population and/or manipulation of human subjects.

2.16 Limitations of the study:

I. Being a purely descriptive study, the study will not explain the etiology of the observations.

II. The research will only be able to describe those elements of the research whose data was readily available through routinely collected data on ARV service statistics. It was initially hoped that the research would also describe viral loads outcomes and the impact of drug use, employment status, and level of education of subjects on clinical and laboratory outcomes. However, this has not been possible because viral loads were not routinely done on every patient and data on drug use, employment status, and education level was not consistently captured by health care workers. These variables were therefore omitted from the study.

III. The findings might have poor external validity because Selebi Phikwe has a high population density domiciled near health facilities, an advantage not shared by other districts that are relatively more sparsely populated.

2.17 Strengths

I. The study was relatively cheap to conduct because it utilized routinely collected data.
II. The study population is the true representation of the actual population because data came from the entire sampling frame (the universe).
III. Since the study is not an intervention but a description of experiences, the results is likely to reflect what would normally happen in the Public Health sector in Botswana.

CHAPTER 3: Results

3.1 Introduction

This chapter discusses outcomes of adult patients started on ART in Selebi Phikwe, Botswana from June 2004 to June 2005. Results discussed here relate to: 1) the total numbers of patients started on ART, 2) pretreatment CD4 counts, 3) CD4 counts at 12 months of ART, 4) death outcomes within 12 months of commencing of ART, 5) basal CD4 counts for patients who died within 12 months of commencing ART, 6) length on treatment before death, and 6) patients lost to follow-up.

3.2 Number of HIV-infected adult started on ART

The public sector ART program in Selebi Phikwe, Botswana initiated a total of 904 HIV-infected adult patients comprising 549 females and 355 males on ART from June 2004 to June 2005. Eligibility for ART was based on a CD4 cell count being less than 200 cells per milliliter of blood and/or presence of an AIDS-defining illness.

Table 1: HIV-infected adult patients started on ART

Age range	Number of patients started on ART	Percentage by age range
15-19	17	1.80%
20-24	38	4.20%
25-29	151	17%
30-34	177	20%
35-39	161	18%
40-44	145	16%
45-49	83	9%
50-54	80	9%
55-59	50	5%
60-64	2	0%
65-70	0	0.00%
Total	904	100.00%

Table 2: Number of patients started on ART disaggregated by age and sex

Age range	Females	Males	Total	% of females	% of males
15-19	9	8	17	53%	47%
20-24	23	15	38	61%	39%
25-29	108	43	151	72%	28%
30-34	121	56	177	68%	32%
35-39	92	69	161	57%	43%
40-44	87	58	145	60%	40%
45-49	47	36	83	57%	43%
50-54	42	38	80	53%	48%
55-59	19	31	50	38%	62%
60-64	1	1	2	50%	50%
65-70	0	0	0	0	0
Total	549	355	904	61%	39%

3.3 Basal CD4 counts for adult patients started on ART

Most adult patients started on ART in selebi Phikwe, Botswana had a relatively low CD4 cellular count. The lowest count recorded was 1 cell per milliliter of blood. The mean count was 54 cells per milliliter of blood. The median count was 25 cells per milliliter of blood.

Table 3: Frequency table showing basal CD4 range for patients initiated on ART

CD4 range	females	Males	Total	% of patients per CD4 band
> 10	227	161	388	43%
ten -25	33	22	55	6%
26-50	65	54	119	13%
51-100	113	68	181	20%
101-200	66	43	109	12%
201-300	32	7	39	4%
Unknown	13	0	13	1%
Total	549	355	904	100%

3.4 CD4 counts after 12 months of treatment

After 12 months of treatment with ART, there was no patient with a CD4 cellular count of less than 50 cells per milliliter of blood. The mean CD4 count rose to 181 and the median to 147 cells per milliliter of blood.

Table 4: Frequency table shows the distribution of CD4 counts in adult patients initiated on ART after 12 months of treatment.

CD4 range at 12 months of ART	Females	Males	Total
< 10	0(0%)	0(0%)	0 (0%)
10 25	0(0%)	0 (0%)	0 (0%)
25-50	0(0%)	0 (0%)	0 (0%)
50-100	15(2%)	8 (1%)	23 (29%)
100-200	230(28%)	157 (20%)	387 (48%)
200-300	124(15%)	76 (9%)	200 (24%)
300-400	48(6%)	51 (6%)	99 (12%)
400-500	32(4%)	7 (1%0	39 (5%)
500-600	20(3%)	9 (1%)	29 (4%)
600-700	13(2%)	3 (0%)	16 (2%)
700-800	11(1%)	0 (0%)	11 (1%)
Total	493(61%)	311 (39%)	804 (100%)

3.5 Mortality while on ART

Of the 904 adult patients started on ART, 84 patients (43 females and 41 males) died within 12 months of commencement of ART.

Table 5: Frequency table showing mortality outcome while on ART

Age range for patients who died	female	Male	Total
15-19	1 (1%)	0 (0%)	1 (1%)
20-24	1 (1%)	0 (0%)	1 (1%)
25-29	10 (12%)	5 (6%)	15 (18%)
30-34	8 (10%)	6 (7%)	14 (17%)
35-39	6 (7%)	10 (12%)	16 (19%)
40-44	5 (6%)	6 (7%)	11 (13%)
45-49	6 (7%)	7 (8%)	13 (15%)
50-54	4 (5%)	4 (5%)	8 (10%)
55-59	2 (2%)	3 (4%)	5 (6%)
60-64	0 (0%)	0 (0%)	0 (0%)
65-70	0 (0%)	0 (0%)	0 (0%)

3.6 Proportion of female who died while on ART

Forty three female patients (8%) died while on ART.

Table 6: Proportion of mortality among females

Total number adult females initiated on ART	549
Total Number of females who died while ART	43
Proportion of females who died while on ART	8%

3.7 Proportion of males who died while on treatment

Forty one male patients (12%) died while on treatment

Table 7: Proportion of mortality among males

Total number adult males initiated on ART	355
Total Number of males who died while ART	41
Proportion of males who died while on ART	12%

3.8 Time on treatment before death

Of the 84 patients who died while on treatment, close to 60% of them died in the first three months of commencement of treatment.

Table 8: Length on treatment before death

	Female	Males	Total
< 1 month	15 (18%)	12 (14%)	27 (32%)
1-2 months	5 (6%)	6 (7%)	11 (13%)
2-3 months	6 (7%)	4 (5%)	10 (12%)
3-4 months	3 (3%)	3 (3%)	6 (6%)
4-5 months	3 (3%)	0 (0%)	3 (3%)
5-6 months	2(3%)	2 (3%)	4 (6%)
6-7 months	2 (3%)	2 (3%)	4 (6%)
7-8 months	1 (1%)	1 (1%)	2 (2%)
8-9 months	2 (3%)	6 (7%)	8 (10%)
9-10 months	1 (1%)	0 (0%)	1 (1%)
10-11 months	0 (0%)	3 (3%)	3 (3%)
11-12 months	3 (3%)	2 (3%)	5(6%)
Total	43 (51%)	41 (49%)	84 (100%)

3.9 Basal CD4 counts for patients who died

Mortality was higher among patients with low basal CD4 counts. Of the 84 patients who died while on treatment, 75 of them had a CD4 cellular count of less than 10 cells per milliliter of blood.

Table 9: Frequency table showing the basal CD4 counts for patients who died

Basal CD4 count for adult patients who died	Female	Male	Total
< 10	39 (47%)	36 (43%)	75 (89%)
10 25	1 (1%)	2 (2%)	3 (4%)
25-50	1 (1%)	3 (4%)	4 (5%)
50-100	2 (2%)	0 (0%)	2 (2%)
100-200	0 (0%0	0 (0%)	0 (0%)
200-300	0 (0%)	0 (0%)	0 (0%)
300-400	0 (0%)	0 (0%)	0 (0%)
400-500	0 (0%)	0 (0%)	0 (0%)
Total	43 (51%)	41 (49%)	84 (100%)

Table 10: Frequency table of Age range of patients who died

Age range for patients who died	female	Male	Total
15-19	1 (1%)	0 (0%)	1 (1%)
20-24	1 (1%)	0 (0%)	1 (1%)
25-29	10 (12%)	5 (6%)	15 (18%)
30-34	8 (10%)	6 (7%)	14 (17%)
35-39	6 (7%)	10 (12%)	16 (19%)
40-44	5 (6%)	6 (7%)	11 (13%)
45-49	6 (7%)	7 (8%)	13 (15%)
50-54	4 (5%)	4 (5%)	8 (10%)
55-59	2 (2%)	3 (4%)	5 (6%)
60-64	0 (0%)	0 (0%)	0 (0%)
65-70	0 (0%)	0 (0%)	0 (0%)
Total	43 (51%)	41 (49%)	84 100%)

3.10 Lost to follow-up

Of the 904 patients started on treatment, 16 (2%) were lost to follow-up

Table 11: Frequency table of age range of patients lost to follow-up

Age range for patients lost to follow-up	Females	Males	Total
< 20 years	0 (0%)	1 (6%)	1 (6%)
20-25 years	1 (6%)	1 (6%)	2 (13%)
26-30 years	2 (13%)	2 (13%)	4 (25%)
31-35 years	1 (6%)	1 (6%)	3 (19%)
36-40 years	3 (19%)	3 (19%)	5 (31%)
41-45 years	1 (6%)	0 (0%)	1 (6%)
Total	8 (50%)	8 (50%)	16 (100%)

CHAPTER 4: Discussion

4.1 Introduction

This chapter discusses clinical and laboratory outcomes of adult patients started on ART in Selebi Phikwe, Botswana from June 2004 to June 2005. The primary outcomes of interest include the following: 1) the total numbers of patients started on ART during the study period, 2) pretreatment CD4 counts, 3) CD4 counts at 12 months of ART, 4) death outcomes within 12 months of commencing of ART, and the lost to follow-up outcome within 12 months of ART. Secondary outcomes include: 1) basal CD4 counts for patients who died within 12 months of commencing ART, 2) length on treatment before death, 3) the gender which presented late for HIV diagnosis and treatment, 4) the gender most in need of ART, and 5) the age range most in need of ART

4.2 Total Number of Patients Started on ART by Age Range: In all, 904 adult patients were initiated on ART in Selebi Phikwe, Botswana from June 2004 to June 2005. The number of adult patients started on ART was relatively small (15%) compared to the estimated number of patients (6,000) in need of ART. The main reason for this low enrollment was the limited capacity of the health system to enroll all the ART eligible adult patients. New ART programs in sub-Saharan Africa where the burden of HIV is high have issues of patient carrying capacity.

4.3 Age Range Most in Need of ART: Of the 904 adult patients initiated on ART during the study period, 689 (representing 76%) were between the ages of 15-49. This finding is consistent with several studies that have shown that the bulk of people with HIV infections are likely to consist of people between the ages of 15-49. Homas Goliber (2010) observes from various studies that both HIV and AIDS strike hardest among people 15 to 49 years. The high burden of HIV among the economically active sub-population has socio-economic consequences on the district and the country. The burden increases medical absenteeism, increases the cost of doing business through new recruitments to replace sick workers and medical bills, and increases the dependency ratio. Additionally this same age group is needed for delivery of health services, including ART. Therefore, this affects the rate of expansion of ART services.

4.4 Gender most in need of ART: Of the 904 adult patients initiated on ART in Selebi Phikwe, Botswana from June 2004 to June 2005, 549 (61%) were females and 355 (39%) were males. These findings are consistent with what has been observed elsewhere that there are usually more females than males infected with HIV. In Swaziland, a small landlocked country where 26.1% of the country's adult population is infected with HIV, women have been particularly affected by the epidemic; among those aged 15-49 HIV prevalence among women is 31%, compared to 20% among men (UNAIDS, 2008).

4.5 Basal CD4 counts (pretreatment CD4 counts): Most adult patients started on ART in selebi Phikwe, Botswana had a relatively low CD4 cellular count (lowest being 1 cell and highest 500 cells). Of the 904 patients initiated on ART in Selebi Phikwe, Botswana from June 2004 to June 2005, 388 (43%) had a CD4 count of less than 10 cells per milliliter of blood; 55 (6%) between 10 and 25 cells per milliliter of blood; 119 (13%) between 26 and 50 cells per milliliter of blood; 181 (20%) between 51 and 100 cells per milliliter of blood; and 161 (17%) above a cellular count of more than 200 cells per milliliter of blood. The lowest CD4 count recorded was 1 cell per milliliter of blood. The mean count was 54 cells per milliliter of blood. The median count was 25 cells per milliliter of blood.

The low basal CD4 count could be accounted for by the fact that this was a new ART program enrolling patients who had been infected for a long time and therefore with advanced HIV. The program only started in 2005 whereas the epidemic had been around since 1986 (Botswana ART Project Description Document, (2001). Other reasons could be that new public sector ART programs may 1) prioritize initiation of patients on ART based on the progression of HIV disease, including CD4 counts, 2) ART services may be centralized thus preventing people from readily accessing ART services, and 3) the levels of education and culture may influence health seeking behaviors. In a study conducted by Mbarara University Teaching Hospital to determine factors responsible for late presentation for HIV diagnosis and treatment, investigators discovered that a lower level of education and long distances from service facilities were associated with late presentation for diagnosis and treatment of HIV.

4.6 Gender which presented late for HIV diagnosis and treatment : Of the 549 female adult patients initiated on ART in Selebi Phikwe, Botswana from June 2004 to June 2005, 325 (59%) had a CD4 count of less than 50 cells per milliliter of blood, and therefore classified as late presenters. Of the 355 male adult patients initiated on ART in Selebi Phikwe, Botswana from June 2004 to June 2005, 237 (67%) had a CD4 count of less than 50 cells per milliliter of blood, and therefore classified as late presenters. In this study, the proportion of late presenters among males was higher than among females. Results from other studies on the gender that presents late for diagnosis and treatment of HIV between females and males have varied from country to country. A study to inform on clinical outcomes for late presenters (CD4s < 50/ml) conducted by Sabin and others in 2004 concluded that late presenters were likely to be female and that mortality amongst late presenters was 13% (Sabin, et al., 2004). In another study conducted in Venezuela to determine late presenters, the study concluded that females rather than males were less likely to present late for care (Bonjour, et al., 2008). Another study conducted by the Mbarara University Teaching Hospital concluded that males were more likely to be diagnosed late than women (50% vs. 36%). Another study to compare the direct cost of medical care in years following the diagnosis of HIV in early and late presenters in Canada showed that late presenters are likely to be men (Krentz, Auld, and Gill, 2004).

4.7 CD4 counts at 12 months of ART: The study shows that after 12 months of ART there was no patient with a CD4 cellular count of less than 50 cells per milliliter of blood. The mean CD4 count rose to 181 and the median to 147 cells per milliliter of blood. This finding is consistent with what has been found by other studies. Investigators note that CD4 counts at the start of treatment although low in most ART programs, have increased in recent year (Nash, 2008). In Cambodia 416 patients with a basal median CD4 count of 11 cells per milliliter of blood, raised their CD4 cellular count to a median level of 154 cells per milliliter of blood after 12 months of treatment with ART (Carter, 2007). In Rwanda, a follow-up of 1,445 patients on ART from January 2004 to December 2005 showed an increase in the median CD4 count by 98 cells per milliliter of blood in 6 months (Ndamage, 2008). A study in Zambia on outcomes for people on ART also showed that despite starting ART at low CD4 cellular counts CD4 counts can still go up.

For patients whose baseline CD4 count was less than 50 cells/ml of blood, the median increase in CD4 counts at one year was 200 cells, while the median increase in patients with a CD4 count of more than 200 cells per milliliter of blood was 162 (Stringer, 2006). In another study done in Botswana by Wester and others (2005) involving 871 patients enrolled on ART at the Princes Marina Hospital (PMH) in Botswana between January 2002 and August 2002 the median increase in CD4 cell counts was 169 cells per milliliter of blood after one year of treatment (Wester, 2005).

4.8 Death outcomes within 12 months of commencing of ART: Of the 904 adult patients initiated on ART in Selebi Phikwe, Botswana from June 2004 to June 2005, 84 patients died, representing 9.2% mortality while on ART. This mortality rate on ART is consistent with many studies. In a study in Malawi to show how ART had reduced all cause mortality, investigators discovered that overall, 8% of AIDS deaths occurred in those who received ART (John, 2008). A study to evaluate the cause of mortality among HIV-infected patients talking ART in Senegal established a mortality of 6.3% among patients taking ART (Etard, 2006).

4.9 Mortality of females to males: Of the 84 deaths that occurred among adults initiated on ART in Selebi Phikwe Botswana, 43 were females and 41 were males. The proportion of mortality was higher in males than females (12% vs. 8%). The most obvious explanation as to why there was a higher proportion in mortality observed in males compared to females was that males presented later than females for diagnosis and treatment of HIV.

4.10 Mortality and basal CD4 count: Of the 84 patients who died while on ART, 75 (89%) started ART with a CD4 count of less than 10 cells per milliliter of blood. This finding is consistent with various other studies which have demonstrated that basal CD4 counts can predict mortality outcomes. Individuals who initiate antiretroviral treatment when they have a very low CD4 cell count or are severely unwell because of HIV often have poor outcomes. Research to date suggests that between 15 and 43% of individuals in resource-limited settings are in this situation when they start HIV treatment (Kigosi,

2009). Recently, a multi-country analysis of outcomes on ART involving 18 sub-Saharan countries showed that the baseline CD4 cell count was the most important predictor of outcomes, with better responses at higher baseline counts. Compared with people with higher CD4 counts, individuals with a CD4 count of less than 50 cells per milliliter of blood were two and half times more likely to die (summary hazard ratio 2.5; 95% CI, 1.9-3.2) (Lawn, 2008). Another study conducted in Zambia demonstrated that one year mortality was 2.3 fold higher for patients who started treatment with a baseline CD4 of less than 50 cells per milliliter of blood compared with those who started treatment between CD4 50 and 200. Predictors of mortality included baseline CD4 counts of less than 50 (Stringer, 2006)

4.11 Length on treatment before death: Of the 84 patients who died while on treatment, close to 60% died in the first three months of commencement of treatment. This finding is consistent with many published materials on mortality for people on ART. Patients starting on antiretroviral therapy in Sub-Saharan Africa have a high mortality, according to a review article published in the October 1st edition of AIDS. Most of the deaths occurred in the first three months of treatment (Nash, 2008)

4.12 Laboratory Monitoring of patients: Because of cost and time constraints associated with monitoring laboratory parameters, viral load testing was only done when required and not routinely

Chapter 5: Conclusion and Recommendations

5.1 Conclusion

This study shows that it is feasible to implement a public sector ART program providing free ART services for free in resource-limited settings such as sub-Saharan Africa. The study also confirms that such programs could have similar outcomes to those programs implemented in the developed world.

5.2 Recommendations

5.2.1 Positive clinical and Laboratory Outcomes: The study, like many other studies conducted in resource limited settings, has demonstrated that public sector ART programs can produce good laboratory and clinical outcomes. The investigator therefore recommends that countries having a high prevalence of HIV should consider scaling-up of ART services because the outcomes are good.

5.2.2 Avoiding Adverse Outcomes: The study supports findings of other studies in demonstrating that mortality is highest in individuals starting HIV treatment with low CD4 counts. The investigator therefore recommends that health systems adopt strategies that encourage initiation of ART when CD4 are still high. Strategies would include but not limited to: 1) scaling up of testing and counseling for HIV to increase the number of individuals knowing their HIV status early, 2) Creating strong linkages between HIV testing and counseling services with laboratory services providing CD4 cytometry, 3) scaling up on the numbers of sites providing ART services, including mobile services, and 4) prompt management of opportunistic infections.

5.2.3 Health Seeking Behaviors: The study also shows that men, rather than women, presented late for diagnosis and treatment of HIV with low CD4 counts. The study recommends that more investigations be done to determine the cause of this behavior to promote equity in seeking HIV care between men and women.

5.3.4 Critical Period: The study shows that mortality is highest in the first three months on treatment. This mortality could possibly be reduced if good quality clinical management is implemented and adhered to in the first three months of ART. Aspects of good clinical management could include but not limited to: 1) prompt diagnosis and treatment of opportunistic infections such as TB, 2) regular follow-up of patients which can range from daily, weekly or every two weeks depending on individual circumstances, 3) checking for evidence of untoward effects of ART, and being alert to the development of the immune reconstitution syndromes (IRS)

APPENDIX 6

REFERENCES

Reference:

1. Achmat, Z. 2002. Most South Africans cannot afford anti-HIV drugs. Commentary. BMJ, vol. 7331, pp. 217-218

2. Ahn, M. J., Grimwood, G., Schwarzwald and Herman, A. 2003. Ethics and the AIDS pandemic in the developing world. JIAPAC, vol. 2 (2), pp. 81-86

3. Akileswaran, Lurie, Flangan, and Mayer. 2010. Lessons Learned from use of Highly Active Antiretroviral Therapy in Africa.

4. Anso, T. 2005. Cape town Times, 22 April, 2005

5. Barth., et al, 2011. Long-Term Outcome of an HIV-Treatment Program in Rural Africa: Viral suppression despite Early Mortality

6. Bartlet, J. G. and Gallant, J. 2004. Medical Management of HIV. 2004 edition. Maryland, USA: John Hopkins University.

7. Botswana. 2002. ARV Project Description for Botswana.

8. Botswana. 2002. HIV/AIDS national surveillance.

9. Botswana. 2003. HIV/AIDS national surveillance.

10. Botswana. 2005. Ministry of Health bulletin

11. Carpenter, C. 2002. Initial antiretroviral regimes: in general three drugs are better than two, and two are better than one. BMJ, vol. 7340 (324), pp. 747-798.

12. Emmelkamp and Rockstroh. 2007.Evolution of HIV Therapy-Literature review

13. Ferrer. 2004. Niverapine containing regimes in HIV infected treatment-naïve patients with CD4 < 200 or less: Research letter. AIDS, vol. 18(12), pp. 1727-1729

14. Hewitt, Smith, Thomson and Walsh. 2002. Missed appointments in HIV clinical practice. International conference on adherence to antiretroviral therapy, 2002, Dallas, USA.

15. Jordan, R., Gold, L., Cummins, C. and Hyde, C. 2002. Systemic review and meta-analysis of evidence for increasing numbers of antiretroviral combination therapy. BMJ, vol. 7340 (324), pp.

16. Kigozi, I.M. 2009. Late-disease stage diagnosis at presentation to an HIV clinic in the era of free antiretroviral therapy in sub-Saharan Africa. Journal of Acquired Immunodeficiency Syndrome, 2009.

17. Kloser, P. C. 2003. Hepatitis, Mental illness and substance abuse: managing the triple-diagnosed HIV patient. IAPAC, vol. 9 (7), pp.147-148

18. Lawn, S.D. 2008. Early Mortality among adults accessing antiretroviral treatment programs in sub-Saharan Africa. AIDS 22:1897-1908

19. Lee Jong-Wook. 2003. Global Health improvement and WHO: shaping the future. The Lancet, Vol. 362, pp. 2083-2088

20. Martin WG Brinkhof[I]; François Dabis[II,I]; Landon Myer[III]; David R Bangsberg[IV]; Andrew Boulle[III]; Denis Nash[V]; Mauro Schechter[VI]; Christian Laurent[VII]; Olivia Keiser[I]; Margaret May[VIII]; Eduardo Sprinz[IX]; Matthias Egger[I]; Xavier Anglaret. 2009. ART-LINC of IeDEA collaboration

21. Miller, M.D. 2004. K65R, TAMS and Tenofovir. AIDS Reviews. 2004; 6: 22-33

22. Nash, D., et al. 2008. Long term immunological response to antiretroviral treatment in low-income countries: a collaborative analysis of prospective studies. AIDS 22:2291-2302

23. Ndamage, F., et al. 2008. Evaluation of clinical and immunological outcomes from national ART program in Rwanda, 2004 to 2005

24. Oyugi and Bangsberg. 2002. Adherence to antiretroviral therapy in Africa: A relationship between household economies. International conference on adherence to antiretroviral therapy, 2002, Dallas, USA.

25. Rathban, C and Farmer, K.S. 2002. Medication adherence rates with Highly Active Antiretroviral therapy and virological response. International conference on adherence to antiretroviral treatment. 2002 December 5-8: Dallas, Texas. USA

26. Sabin, A.C. 2004. Late presenters in the era of HAART: Uptake and responses to ARV. AIDS, vol. 18 (16), pp. 2145-2151

27. Sabin, A.C and Philips, N. P.2001. Treatment Comparison in HIV Infection: The benefits and limitations of observational studies. The Journal of Antimicrobial Chemotherapy, vol. 47, pp. 371-375.

28. Schneider, H. 2001. Implementing AIDS policy in the post-apartheid South Africa. Social Sciences and Medicine, vol. 52 , pp. 723-731

29. Schneider, H. 2002. Denial and Defiance: a socio-political of AIDS in South Africa. AIDS, vol. 16 (suppl 4), pp. s45-s51.

30. Smith, C. J. 2004. Low viral loads at 4 weeks of antiretroviral therapy are a predictor of viral loads at 24 weeks. Journal of Immunodeficiency syndrome, vol. 37, pp. 1155-1159

31. Stringer. 2006. Rapid expansion of HIV treatment Services in Africa feasible, with good patient outcomes

32. Travis, P., Bennert, S., Haines, A., Pang, T., Bhutta, Z., Hyder, A.A., Pielemeier, N.R., Mills, A. and Evans, T. 2004. Overcoming health-systems constraints to achieve Millennium Development Goals. The lancet, vol. 364, pp. 900-906.

33. UNAIDS. 2001. Together we can: Leadership in a world of AIDS. June 22, 2001. Geneva, Switzerland. http/www.unaids.org.UNGASS/index.html

34. World Health Report. 2003