"THE MODELS OF CARE" PROJECT

An Analysis of the National Antiretroviral Treatment Programme, Masa, 2007-2011:

Programme Effectiveness,
Costs to the Country,
and Clinical Effectiveness

Final Report

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Government of Botswana

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A joint project of

BOTSWANA MINISTRY OF HEALTH
MASA
BOTSWANA–HARVARD AIDS INSTITUTE PARTNERSHIP (BHP)
HARVARD SCHOOL OF PUBLIC HEALTH (HSPH)
AFRICAN COMPREHENSIVE HIV/AIDS PARTNERSHIPS (ACHAP)

MINISTRY of HEALTH
Masa Antiretroviral Therapy
BOTSWANA HARVARD AIDS INSTITUTE PARTNERSHIP FOR HIV RESEARCH AND EDUCATION
HARVARD SCHOOL OF PUBLIC HEALTH
ACHAP

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ABBREVIATIONS

ACHAP: African Comprehensive HIV/AIDS Partnership
AIC: Akaike Information Criterion
ART: Antiretroviral Therapy
ARV: Antiretroviral drugs
BAIS III: Botswana AIDS Impact Survey (III)
BHP: Botswana-Harvard AIDS Institute Partnership
BMI: Body-mass index
cART: combination antiretroviral therapy
CD4: Cluster of Differentiation 4
CMV: Cytomegalovirus
D4T: aka Stavudine, *Zerit*; a NRTI
eGFR: estimated Glomerular Filtration Rate
GFR: Glomerular Filtration Rate
HAART: Highly Active Antiretroviral Therapy
HIV-1C: Human Immunodeficiency Virus Subtype 1 Group C
HIV/AIDS: Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome
HIVAN: Human Immunodeficiency-associated neuropathy
HRH: Human Resources for Health
HSPH: Harvard School of Public Health
IDCC: Infectious Disease Control Centre
IQR: Interquartile Range
KITSO: Knowledge, Innovation & Training Shall Overcome AIDS Program
LPV/r: lopinavir/ritonavir
M&E: Monitoring & Evaluation
MASA: "New Dawn", in Setswana. The name for the National ART Programme of the Ministry of Health of Botswana
MLG: Ministry of Local Government
MOC: Models of Care
MoH: Ministry of Health
NNRTI: Non-nucleoside Reverse Transcriptase Inhibitor
NRTI: Nucleoside Reverse Transcriptase Inhibitor
OI's: Opportunistic Infections
OPD: Outpatient Medical Department
PEPFAR: President's Emergency Plan for AIDS Relief
PMTCT: Prevention of Mother to Child Transmission
RCT: Randomized Controlled Trials
RNA: Ribonucleic Acid
TTR: Treat, Train, Retain
UN: United Nations
UNDESA: United Nations Department of Economic and Social Affairs
UNICEF: United Nations International Children's Emergency Fund
WHO: World Health Organization

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EXECUTIVE SUMMARY

The purpose of the Models of Care (MOC) project was to improve the Botswana National Antiretroviral Treatment (ART) Programme (*Masa*) through evaluation of the program scale-up, and inform decisions regarding national guidelines before and after treatment initiation. The project consisted of three parts: 1) Evaluation of the *Masa Programme* at the individual patient level; 2) Costing of the *Masa Programme* over time and; 3) Creation of specific clinical cohorts to answer Botswana-specific care and treatment questions.

Overall, the evaluation of the *Masa Programme* at the individual level showed a program that has good overall clinical outcomes and that is improving those outcomes as it matures. The regression analysis of the *Masa* data showed that the *Masa Programme* improved over time (the probability of death for an individual patient decreases with time and with Year of Enrollment in the program). The analysis did not find evidence indicating superiority of tenofovir/FTC over zidovudine/3TC in terms of survival, nor superiority of efavirenz over nevirapine. However, our findings indicate that chance of survival for the patients on didanosine is significantly less than those on Tenofovir. An important finding, in this part of the study, was that there are significant differences among the health districts in terms of survival, which requires further investigation.

The costing exercise of the *Masa* Programme was done from 2009-2010. This exercise estimated that the cost of treatment per patient would be $357.00 USD in 2011 and projected it to reach $430.00 USD in 2014. The estimate for the total cost of the program in 2010 added up to $53 million USD, which in 2014 is projected to reach $99 million USD. The costing exercise highlighted that the three primary drivers of the provision of ART in the *Masa Programme* are ART drugs, laboratory tests, and personnel. With different scenarios evaluated in the exercise, planning for future costs and needs is possible.

The third component of MOC was the creation of specific clinical cohorts. The results from our first clinical cohort of individuals living with HIV being followed prior to qualifying for ART themselves, showed that in Botswana with HIV-1 subtype C infection, the CD4 count had different patterns of decline by baseline CD4 and RNA category over time. Also, overall CD4 counts declined over time in a nonlinear fashion. We found baseline RNA, though, is a good predictor of rate of CD4 count decline or disease progression. Therefore, by considering these patterns of CD4 cell count over time, the composite criteria of CD4 and RNA for treatment initiation could be considered in Botswana.

With a second clinical cohort, which followed individuals initiating the newer first-line regimen and treatment guidelines in Botswana, we confirmed the findings of other studies with regards to tenofovir renal toxicity. The magnitude of the risk for renal toxicity found, though, warrants further evaluation of the toxicity monitoring capabilities in the *Masa Programme*. Both of these clinical cohorts helped provide costs and outcome data for overall evaluation and costing of the *Masa Programme* noted earlier.

INTRODUCTION

From 2007-2011, Harvard School of Public Health (HSPH) and the Botswana-Harvard AIDS Institute Partnership (BHP) have worked with the Ministry of Health (MoH) and the African Comprehensive HIV/AIDS Partnership (ACHAP) in Botswana to examine the effectiveness of the HIV healthcare service delivery model in Botswana. To approach this issue from different angles, the "Models of Care" (MOC) Project was organized into three arms to study (1) programmatic effectiveness, (2) cost, and (3) clinical effectiveness.

The studies under the MOC Project are meant to inform decisions regarding the efficacy, long-term financial sustainability, feasibility, and effectiveness of existing models of clinical healthcare delivery and laboratory monitoring in Botswana. New antiretroviral treatment (ART) regimens, expanded treatment and laboratory monitoring of HIV/AIDS care, and changing clinical guidelines all warrant evaluation in the Botswana setting. In addition, as with healthcare systems worldwide – variations in healthcare provision in various parts of the country may affect population-level and individual-level health outcomes. Results of the studies in the MOC Project reveal some of the long-term clinical benefits and problems associated with ART in settings in Africa. The studies further contribute to the existing empirical evidence supporting the overall success of the MoH's National ART Programme, *Masa*.

The three main and interrelated areas of evaluation in the MOC Project involve:

1. The Evaluation of the National ART Programme, *Masa*: Evaluating the *Masa Programme* data on patients enrolled in the *Masa Programme* at ARV public treatment sites and via the Public Private Partnership programme; and predicting the effect of contextual factors of the health system on clinical outcomes;
2. The Costing of the *Masa* Programme: Tracking and costing healthcare resource utilization of ART programs in Botswana, and;
3. The MOC Clinical Cohorts: Determining long-term clinical, immunological, and virological benefits of the newest Standard of Care practices of the *Masa Programme*, both for patients prior to needing ART and for patients on ART.

All previously listed objectives of the MOC Project can be divided into these three areas, although in previous reports the order of the evaluations covered is different, depending on when the results became available and were reported to the Ministry of Health.

EVALUATION OF THE NATIONAL ANTIRETROVIRAL TREATMENT PROGRAMME (*MASA*)

Background

At the beginning of the MOC study in 2007, the major challenge for the national programme was universal coverage. From 2004 to 2006, there was rapid scale-up of the national program. The Ministry of Health (MoH) and Ministry of Local Government (MLG) had developed an aggressive plan to upgrade the satellite clinics to full-service facilities which would enable them to prescribe and dispense antiretroviral drugs while maintaining the 'site system' for reporting and providing support services. The MoH and MLG identified 128 clinics for upgrading by the end of the fiscal year 2008/9 and set a goal of 600+ scaled-up clinics by 2013, as indicated in the National Development Plan 2009-2013.

In developing countries, and especially in sub-Saharan Africa, the lack of qualified health workers was recognized as a crisis by the international community. Deficiencies in financial and human resources were strongly limiting coverage of essential care in public health services. In HIV/AIDS care, especially in Botswana, the scale-up of the national antiretroviral treatment (ART) programme (*Masa*) in 2004 further highlighted the gaps in human resources for health care. The scale-up of HIV/AIDS care, in particular, posed challenges for health systems that were already struggling with an absolute shortage of qualified health staff. Following the World Health Organization's (WHO) Treat, Train, Retain (TTR) initiative, task sharing Botswana had received increasing attention as a measure to allow ART roll-out in contexts of shortages in human resources.

The original question prompting the *Masa Programme* study stemmed from the concept of task-shifting. In task-shifting, the tasks that are normally completed by a physician may be delegated to a nurse after the nurse has received specific training. For example, some nurses were trained to prescribe and refill prescriptions for patients who have been initiated, and they are called "Nurse Prescribers." Some nurses were trained to dispense ARV drugs, and were referred to as "Dispensing Nurses." Task sharing is meant to reduce costs, while maintaining the same quality of care. Botswana continues to have low physician to patient ratios, and the majority of physicians are immigrants. It was anticipated that the situation could become exacerbated as increasing numbers of persons attend outpatient clinics for HIV-related care and treatment while these medical wards and outpatient medical department (OPD) clinics remained over-capacity. A solution to these growing concerns was a nurse-centered delivery care model, which was piloted in Gaborone with the anticipation of replication throughout the country.

Part of the original MOC design was intended to evaluate healthcare delivery models to support recommended changes in operational strategies for improvement in the implementation of the

Masa Programme. The original study was to develop two demonstration cohorts – an observational cohort of the patients in *Masa Programme* (*Masa observational cohort*), and another cohort of *Masa Programme* patients receiving HAART via nurse-centered care (*Masa demonstration cohort*).

However, the roll-out of the task-shifting program in Botswana was not carried out in a distinct pattern of certain clinics having "task-shifting" and other clinics not having this program, so it was not possible that the impact of such a program could be measured accurately within the time frame of the Models of Care Project, which led to the revision of the scope of the Models of Care Project.

In the revision process, the Harvard team worked with the teams in the Ministry of Health (MoH) and in ACHAP to ensure that the overall objectives of the study were still met and even broadened in scope. Going back to the main premise of the study, we looked at the efficiency and effectiveness of the existing clinical healthcare delivery system, involving all the clinics and patients in the evaluation, not just the earlier demonstration cohort comparison.

Offering HIV/AIDS care that includes ART is far more complex than simply dispensing pills and prescribing refills. One of the main concerns related to task-shifting is how to maintain quality of care. Our challenge was how to define quality of care and how to measure it. The most important indicator for quality of care in patients with advanced AIDS is commonly considered to be survival. Therefore, we set about doing a multilevel analysis looking at the correlation of human resources for health (HRH) and survival in the *Masa Programme*. It is important to see what factors can explain variation in patients survival.

The Monitoring and Evaluation Unit[1] quarterly data summary reports have shown variations in site-specific performance indicators including retention rates, mortality, median CD4 changes, and consistency in reporting cohort data and CD4 count results. With limited data on site characteristics, and type of services provided, it was difficult to systematically interpret site-specific program performance. Considering the challenges for the analysis at site level, we decided to look at the differences in mortality rate and hazard rate at population and individual levels respectively. In this way, the MoH could better plan for the districts to fulfill needs and improve care, treatment, and prevention. We expected that the results would also help determine any correlation between individual characteristics and program performance, also with the overall goal of program improvement at the district level and beyond.

[1] The Monitoring and Evaluation Unit at the Ministry of Health is part of the Department of HIV/AIDS Care and Treatment. This unit is in charge of the data warehouse that receives all the data coming from health facilities providing ART.

To ensure effective coordination of this effort, all the processes were conducted under the direct supervision of the Directors of Department of HIV/AIDS Prevention and Care and the department of Clinical Services within the MoH, who have an excellent understanding of the *Masa Programme* and its site specific activities. The selection of data points was completed jointly by MOC staff and that of MoH during the first quarter of 2009. Additional information was obtained by interviews with the facility personnel, PEPFAR Master Trainers or MoH officials.

Data Acquisition and Challenges

Working with the individual level data required acquisition of the approval from the Human Subject Committee both at Harvard School of Public Health and at the Botswana MoH, which we received in mid-2008. We immediately started discussions with the MoH for transfer of the data which were already in the data warehouse at the Monitoring & Evaluation Unit in the MoH. However, as a result of staff movement within the M&E Unit, we actually received the data in the 2nd quarter of 2009.

One of the challenges was to prepare the raw data for the analysis. The database constituted many overlapping datasets. Though not immediately apparent to the team, interim and final analysis was complicated by the need to merge several data sets. Harvard staff spent approximately eight months writing programs to clean the data, so that it was ready for analysis.

The following is the description of the first batch of *Masa Programme* data which was received for analysis.

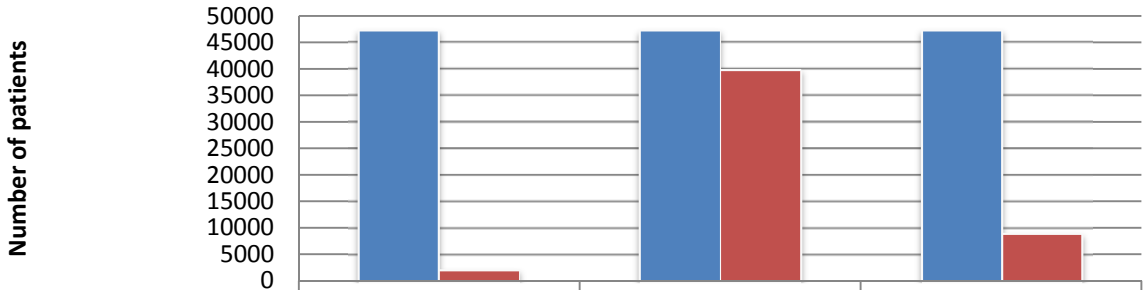
First Database Characteristics

In this dataset, there were a total of 47,226 unique patient records. The records for these patients included demographic data such as age, sex, and hospital locations, at a minimum. Of this total, 39,783 had a recorded CD4 count at baseline, 2,182 had a baseline viral load measurement, and 8,894 had first-line medication information.

There were 42,310 additional patients with more than one record in the dataset (total of 190,587 observations). The number of observations ranged from 1 to 19 per unique patient, with an average of 5.3 observations per person. Approximately 55% of the 33,955 records contained from 1 (included) to 4 CD4 cell count observations (which means 45% had more than 4 CD4 observations). In this dataset, 23,813 patient records included one or more viral load observations, for a total of 55,659 observations. The number of viral load observations ranged

from 1 to 18 per unique patient, with an average of 2.3 observations per person. Approximately 60% of the 23,813 records contained between 1 and 2 viral load observations.
The total expected number of observations for CD4 cell count and viral load were calculated using the Botswana ART guidelines at the time, which specified that these tests should be performed once every three months, for a total of 4 per year per test type. In our study, based on the duration patients stayed in the study, the total expected observations were about 357,000 for both CD4 and viral load over six years. The actual recorded observations were approximately 199,000 (55.7% of the expected) for CD4 cell count and 56,000 for viral load determinations. These numbers are related to the longitudinal dataset. However, even when looking at the baseline characteristics, there is a difference in the actual number of observations compared to the expected number, due to missing data.

Figure 1: Comparing the Actual vs. Expected Data at Baseline for Analysis



	Baseline HIV viral load	Baseline CD4 count	1st-line medication
Total study population	47226	47226	47226
Available baseline data	2182	39783	8894

As one can see in Figure 1, the number of the observations in the database was much less than what we expected. Therefore, an updated version of the database was requested in the spring of 2010. After a long period of time, a new database was received in March 2011, which only contained data from people age 18 and older (in contrast to the first batch which contained children as well).

Revised and Updated Database Characteristics (March 2011)

In the raw data file, there were 6,950,413 observations. In order to clean the data, we had to break the data into different files based on type of service (for example: weight, CD4,

hemoglobin, type of drug, death, etc.). These files were then cleaned before merging to create the final analysis data set.

We decided to use the following variables based on usefulness in our anticipated model, and perceived reliability of the data: CD4, drugs (zidovudine, tenofovir, d4t, nevirapine, efavirenz), hemoglobin, and "opportunistic infection." We discovered that opportunistic infection was not collected, and instead, reflected medication adverse events (i.e., toxicity). Death was our main outcome variable. We cleaned the data to eliminate duplicate observations, missing observations (i.e. the event type was indicated as CD4, but no CD4 value was entered), dates outside the plausible range (i.e. those before 2002, and those after December 31, 2010), implausible values (i.e. negative hemoglobin values), or observations within a short period (i.e. 2 CD4 measures in the same day).

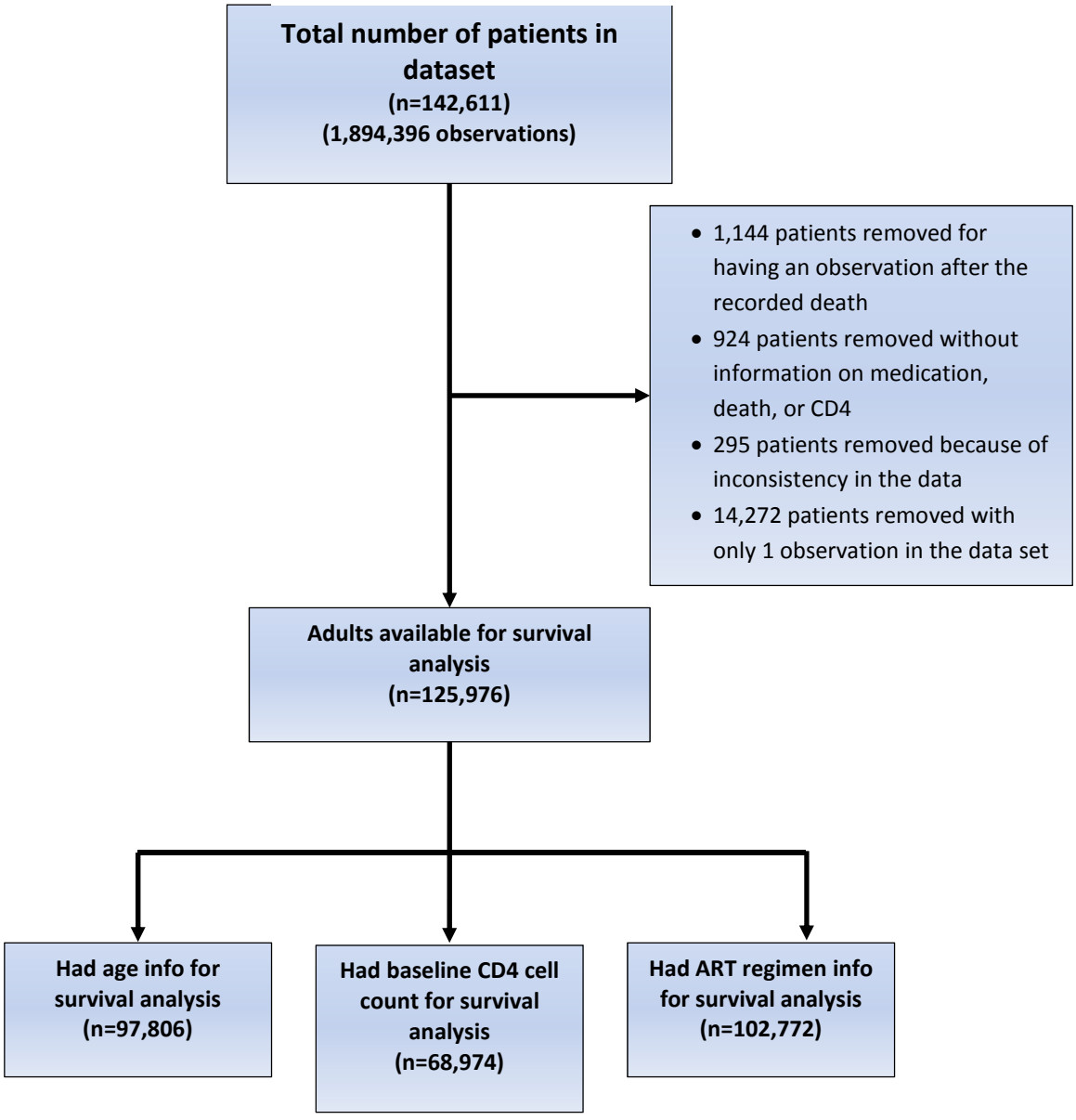
Additionally, to reduce the amount of missing data, data sets were merged based on patient ID, year, and quarter rather than the exact date of observation. Data sets with the following number of observations and patients were generated prior to merging:

Table 1

	Drug	CD4	Death	Hemoglobin	Toxicity (OI)
Number of *observations* before cleaning	660,701	811,172	13,209	567,277	4,185
Number of *unique patients* before cleaning	103,921	139,338	13,002	105,668	1,608
Number of *observations* after cleaning	583,215	689,809	12,913	426,004	3,550
Number of *unique patients* after cleaning	103,921	138,353	12,913	103,115	1,608

Once the data sets were merged, the data needed to be cleaned again to determine what was happening when death wasn't the last observation for a patient (i.e. drug, cd4, hemoglobin observations reported after the death was reported). The resulting data set had 142,611 patients which comprised 1,894,396 observations. Of these patients, 11,251 had their death recorded in the data set.

Figure 2: *Masa Study Flow*



Data Analysis and Findings

We evaluated the effectiveness of the national program using the multivariable regression analysis of 49,000 participants able to be evaluated, controlling for all the baseline characteristics including, sex, age, CD4 cell count, duration of treatment, year of initiation, first-line medication (NRTI and NNRTI), and we found statistically and clinically significant correlation between the district where the patient receives care, as well as the initiation year, and the probability of death. Comparing the odds ratios of districts, with Gaborone district as the reference group, showed that patients who receive care in the Gaborone district face the lowest odds of mortality. Gaborone is the capital with one of the two national tertiary hospitals. The findings indicate that if for example, two women, one in Gaborone and one in Kgalagadi North, of 25 years of age with baseline CD4 count 150, received the exact same regimen, the chance of survival for the one in Gaborone is several times higher. In the same vein, if the same two women with the same characteristics started treatment in the same place at different times, the woman who started in the later years of the program would have a better chance of survival. While this is an important finding, the most important question from a health policy perspective is to find the reason behind this wide variation in mortality. There is evidence that there is greater heterogeneity between the districts than there is within them, which could be due to material deprivation that is associated with health, or lack of training of health care professionals within regions.

In this analysis we had two time variables: treatment duration and year of treatment initiation. The duration of treatment is specified in the model as a cubic function to capture the effect of adherence and severe adverse events, while the year of initiation, a dummy variable, is associated with survival, even when we control for the duration of treatment. Since the year of treatment initiation variable captures the unobserved heterogeneity in that year, it can be interpreted as the effect of different policies, guidelines, or infrastructure on treatment outcomes.

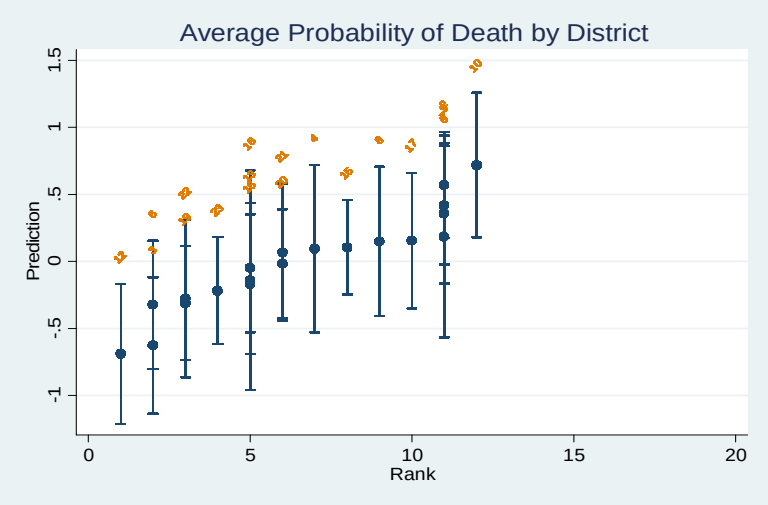
The advantage of this study is to distinguish contextual from compositional effects. The notions of contextual and compositional effects have general relevance and they apply not only when the focus is upon context as geographical setting but also when context is seen in terms of administrative (health authority districts) and temporal (different time periods). The findings of the current study indicate that there are extremely important implications for health services research in each one of these contextual factors as the probability of death among the patients' changes with time and place of services. Variations in the performance of health service activities between different provider units (i.e. mortality) can be attributed to both the type of clients particular units serve ("compositional" effects) as well as the nature of the environment from and in which the service is provided ("contextual" effects). In order to establish how well a particular institution is performing, adjustments must be made for the type of people it serves[2].

[2] Goldstein, H. and Spiegelhalter, D. (1996) League tables and their limitations: Statistical issues in comparisons of institutional performance. Journal of the Royal Statistical Society, Series A 159, 385-443.

Thus, performance measures are needed which are able to separate compositional from contextual effects.

Another interesting finding of this study is that the adjusted mortality odds ratios for people on efavirenz were **not** different from those who used nevirapine, which is in contrast to findings of several clinical trials. This finding needs further investigation.

Figure 3



The basic finding from this work was that place-based contextual factors are much more important for mortality than have previously been appreciated. As can be seen, even when patient level factors were taken into account, district differences in mortality both clinically and statistically were significant. Thus, on the basis of this work it seemed that geographical variations in mortality in Botswana were, to a large degree, due to varying contextual factors. The results show there is much greater variation in mortality between districts than between individuals. (The numbers in orange in Figure 3 indicate district codes.)

The shortcoming of this study is that there are a significant number of missing values. This has created gaps in information regarding patient medication, death, and loss-to-follow-up which are crucial for the analysis. Filling in the information gaps will add precision to our estimates of program effectiveness. The analysis will then be more useful to the planning objectives of the MoH in Botswana.

Estimating the Cost of ART provision to the Government of Botswana in the *Masa* Programme (2010-2014 PROJECTION)

Introduction

The Botswana government has demonstrated a clear and solid commitment to providing ART to people living with HIV/AIDS. Total expenditure on health as percentage of GDP increased from 5% in 1999 to 7.2% in 2006[3]. Underlining this trend, in 2002 the government implemented the *Masa* ART programme. The *Masa Programme* provides ARV treatment to more than 105,000 people[4] living with HIV/AIDS in the country. Botswana has taken important steps on many other issues including development of clinical protocols, training curricula, eligibility criteria, and management systems to ensure a successful ARV treatment program.

The Botswana MoH asked for costing projections of *Masa* over the next five years with the hope that it could offer valuable recommendations to help ensure maintenance and expansion of the *Masa* Programme. The objectives of this costing exercise included the estimation of costs of continuing to provide, and expand, ART in the public sector in Botswana through *Masa*. Specifically, the findings will allow programme planners and policymakers to look at the total programme cost[5] and human resource requirements of providing and scaling-up ART in the public sector.

Data

While most programme costs are incurred at the hospital or clinic levels, we collected cost information centrally, as it is easier to obtain from a centralized point than from dispersed units. For practical purposes, much of our information has been collected from sources within the Ministry of Health. Specifics about the data source of each cost input will be mentioned in the Methodology section.

Demographic data was obtained from documents available from the Central Statistics Office, as well as from statistical databases compiled by the UNDESA Population Division (World Population Prospects report, 2008 Revision); the World Bank (2008 World Development Indicators), UNICEF, and the 2009 Botswana AIDS Impact Survey (BAIS III). The most recent population-based prevalence and incidence were estimated in the Botswana AIDS Impact Survey

[3] WHO Statistical Information System (WHOSIS) http://www.who.int/whosis/
[4] Botswana MoH, Division of Monitoring & Evaluation, 2009
[5] Program costs are outlined in the model descriptions

(BAIS III) of 2009. This report factors in an overall prevalence of 17.6%, and incidence of 2.9% (results from BAIS III). Additional epidemiologic information was provided by UNICEF[6].

Methodology

HIV services cover a broad range of activities, including prevention services for uninfected people, treatment and care services for people living with HIV, and support services for people affected by HIV. In order to do the costing exercise we followed the basic formula that

COST=QUANTITY * PRICE

The most challenging parts were to calculate the number of people eligible to be on treatment; number of people who will be added to the pool and what kind of care (preventive, treatment, etc.,) do they need. Last, but not least, how much each service would cost needed to be determined. To deal with these challenges we formulated four models based on the scope of the activities:

a. Demographic Model
b. Epidemiological Model
c. Medical Model
d. Costing Model

The formulation of the models involved selecting the relevant indicators. This selection was accomplished through consultation with experts in the area and review of documents and guidelines. The above models were carried out sequentially, as each model supplied information that was relevant to the next.

The Demographic Model needed to be developed first. This model was important because it provided information on the entire Botswana population. At this stage we used the data from the Botswana Central Statistical Office. The next step was to calculate the rate of change in population (population growth) using fertility rate, and crude birth rate (births/1000 pop).

The Epidemiological Model was needed to estimate how many people are eligible for prevention and treatment services. This model was used to estimate the following:

- Number of people who needed counselling services
- Number of people eligible for first line of treatment
- Number of people eligible for the second line of treatment (viral failure, drug related toxicity, and treatment failure)

[6] UNICEF <http://www.unicef.org/infobycountry/botswana_statistics.html> Accessed: 9-28-09

- Number of cases with opportunistic infection
- Number of people with co-morbidities
- Estimate the number of new cases (incidence)

The Medical Model looked at the healthcare infrastructure and treatment protocol of the country. It enabled us to estimate the costs associated with each part of the program. To develop this model we needed to know:

- Tests (HIV Screening tests, HIV Confirmation tests, Pregnancy tests)
- ART protocol (First line, Second line, Paediatric, PMTCT interventions)
- Opportunistic infection protocols
- Types of health facilities providing HIV/AIDS related care (referral hospital, primary hospital, IDCC clinics, satellite clinics)
- Health care providers in each facility (physicians, nurses, counsellors, or community health workers)

The Costing Model detailed the actual costs and standard costs of the resources, including the following:

- Staff compensation (monthly compensation by type, number and cost of training modules each group needed for Master Trainer Program and KITSO, turnover rate
- Capital items (buildings, equipment, vehicles)

Results

Our costing exercise produced two primary outputs for the *Masa* Programme over the time period 2009-2014: 1) total per patient cost of HIV care and treatment; and 2) total projected cost. To make these estimations, we pooled demographic, epidemiologic, and cost data for Botswana to formulate a model estimating costs in the *Masa* Programme from 2009-2014. All calculations were performed in US dollars.

We began by projecting *Masa* enrollment for each year. We then conducted a series of calculations with the five primary *Masa* cost inputs included in the projections. The five largest cost drivers of *Masa* are ART drugs, laboratory tests, medical visits, opportunistic infections, and infrastructure. The calculations performed to factor in each of these cost inputs are outlined below.

Masa Programme Enrollment

In order to estimate the costs associated with the national HIV/AIDS treatment program, we needed to estimate the number of people who may seek such health care services. This estimation requires taking both the demographics of the country as well as the epidemiology of the AIDS epidemic into account.

Table 2 shows the current estimations of HIV prevalence in Botswana broken down by age, group, and gender. At the time of the analysis, approximately 105 thousand (105,286) patients had been enrolled into the *Masa* Programme. Enrollment data for *Masa* was obtained from the Ministry of Health and the PEPFAR Monitoring and Evaluation data.

Table 2

	Prevalence [Number, %][7]					
Age Group	**Male**	**Male%**	**Female**	**Female %**	**Total**	**Total %**
00-04	747	2.3	646	2.1	1,393	2.2
05-09	2,800	4.6	2,986	4.8	5,786	4.7
10-14	2,151	3.5	2,127	3.5	4,278	3.5
15-19	1,188	2.4	2,720	5.0	3,908	3.7
20-24	3,419	7.4	9,644	16.0	13,063	12.3
25-29	7,682	16.0	20,051	33.9	27,733	25.9
30-34	11,437	28.6	23,582	48.9	35,019	39.7
35-39	10,455	37.3	16,836	42.8	27,291	40.5
40-44	10,720	43.6	12,484	38.4	23,204	40.6
45-49	5,292	27.7	9,490	31.2	14,782	29.8
50-54	4,162	28.8	4,872	22.2	9,034	24.8
55-59	2,240	19.5	4,265	25.1	6,505	22.8
60-64	1,249	16.7	1,361	14.4	2,610	15.4
65+	3,248	12.6	2,979	8.8	6,227	10.4
Total	**66,790**	**14.2**	**114,041**	**20.4**	**180,831**	**17.6**

Table 3: *Masa* enrollment estimates

Year	Total *Masa* Enrollment
2009	105,286
2010	124,486
2011	143,686
2012	162,886
2013	182,086
2014	201,286

[7]BAIS III 2008, Central Statistics Office (May 2009).

The Ministry of Health provided us with the monthly enrollment numbers from 2002 to 2009. We used the average number of patients added to *Masa* each month (1,600), from January - July 2009 (July being the last month in 2009 that data was available at analysis) and assumed that the enrollment will increase constantly. This monthly enrollment increase brings the additional annual enrollment to 19,200 patients. Table 3 depicts the estimated enrollment for each year.

ART Drugs

The ART drug costs used in our model were provided by the MoH. The regimens we used are based on the 2008 Botswana National Guidelines. Currently, the first line recommendation is Truvada + NNRTI, but those who are still stable on the previous first line, Combivir + NNRTI, are recommended to remain on that line.

Even though Botswana currently receives the majority of its ART drugs through donations, it is important to include the price of drugs in these cost projections. This will allow Botswana to have an idea of what their total *Masa* cost will be if/when they are no longer able to receive the drugs through donations.

Using the individual current drug costs received from the Ministry of Health, we calculated the cost of both first and second line regimens. The regimens selected were from the Botswana National HIV/AIDS Treatment Guidelines: 2008 Version[8]. The first line regimen currently consists of one of the following two combinations: 1) Truvada (tenofovir disoproxil fumarate + emtricitabine) + efavirenz or nevirapine; 2) Combivir (lamivudine + atazanavir) + efavirenz or nevirapine. The second line regimen prescribed most frequently is Truvada (tenofovir disoproxil fumarate + emtricitabine) + lopinavir/ritonavir.

Regarding the first line regimen options, treatment naïve patients are prescribed Truvada + efavirenz or nevirapine. The 2008 Guidelines recommend that patients already receiving the Combivir + efavirenz or nevirapine first line regimen switch to the Truvada regimen over time. Our estimates factor in that 90% of the patients receiving first line treatment are taking the Combivir regimen, leaving 10% on Truvada. We estimate that the percentage of patients on the Truvada regimen will increase annually and reach 65% by 2014 (due to viral failure from Combivir and new patients starting on Truvada). The calculations performed for ART drug costs for each of the five years included were done using a weighted average of the regimens.

Another element factored into our calculations is that the cost of efavirenz, Atripla, and pediatric ART regimens are currently donated. We estimate that Botswana will assume the cost of

[8] Botswana Ministry of Health, Department of HIV/AIDS Prevention and Care

efavirenz and pediatric regimens will increase incrementally by one-third over the next three years (33% in 2010, 66% in 2011, and the full cost from 2012 onward).

Laboratory Tests

Using the 2008 Botswana National HIV/AIDS Treatment Guidelines, we factored in the most important laboratory tests that a patient on ART typically needs, such as CD4, viral load, full blood count, chemistry, and liver. The Guidelines state that each patient is to have their CD4 counts and viral load tests done twice per year while the remaining tests are typically given once per year. We obtained the cost of laboratory tests from the prices in our clinical cohorts. In order to calculate the annual lab test expenses that an average patient in the *Masa* Programme would incur, we calculated the cost of each test multiplied by the frequency that test would be administered (see Table 4 below).

Table 4: Annual Laboratory Test Costs Per Patient

Test	Cost ($US)	Frequency	Total ($US)
CD4	6	2	12
Viral Load	35	2	70
Full Blood Count	3	1	3
Chemistry	7	1	7
Liver	5	1	5
Total laboratory tests			**97**

The total annual per-patient laboratory test cost is $97. We held this number constant for each of the five years (2009-2014).

Medical Visits (Personnel)

The personnel expenses related to necessary medical visits include the staff time of medical, administrative, and supportive staff. The specific staff classifications we included are: doctors, nurses, pharmacy technicians, pharmacists, lab technicians, and counselors. For each staff type, we used the current (2009) average hourly wage we received from the Ministry of Health. We factored that each *Masa* Programme patient will be seen by doctors and nurses twice per year. The pharmacy technicians and pharmacists time is needed in smaller increments as patients come in for refills monthly. We also included twenty-percent for overhead (which includes logistics, administrative and ministerial official expenses).

Table 5: Medical visit costs per patient (2009)

Staff	Average Hourly Wage ($US)
Doctors	19.5
Nurses	12
Pharmacy Technicians	10
Pharmacists	10.5
Lab Technicians	10
Counselors	8
Total personnel	70
Overhead	20%
Total medical visit costs	**84**

The total personnel and overhead costs for medical visits in 2009 is $84 per patient per hour of service (see Table 5). An annual five percent salary increase was factored in for each year from 2010-2014.

Opportunistic Infections

Our prevalence estimates for high-prevalence opportunistic infections (OIs) comes from clinical cohorts and *Masa* Programme data. The six major opportunistic infections and their prevalence over a one year period included are: pneumonia, herpes simplex virus, tuberculosis, neurological disease, mucocutaneous candidiasis, and CMV retinitis.

Table 6: Opportunistic Infections

Opportunistic Infection	prevalence
Pneumonia	8.00%
Herpes Simplex Virus	7.69%
Tuberculosis	7.23%
Neurological Disease (Peripheral Neuropathy)	6.62%
Mucocutaneous Candidiasis / Oral Candidiasis	3.54%
CMV Retinitis	0.15%

The costs for treatment of the opportunistic infections are estimates derived from the International Drug Price Indicator Guide (2008) by Management Sciences for Health. We used the median buyer price per unit of medication when more than one price was available, and we calculated the costs according to the 2008 Botswana National Guidelines for treatment of opportunistic infections.

We used the 2008 National Guidelines to determine the frequency of necessary diagnostic tests and the drug regimen treatment options. The first step was to calculate the cost of the

recommended drug regimens. The next step was to include the cost of any additional medical visits required for specifically treating the OI. This number differed depending on the severity of each OI. For these medical visits, we used the same personnel hourly wages previously described in the *Medical Visits* section. We estimated that the included overall medical visits cost included both outpatient and any needed inpatient care. An example of how each OI cost was calculated is illustrated in Table 7, which estimates the annual cost for a patient with tuberculosis.

Table 7: Annual Tuberculosis Cost Per Patient[9]

Expense	Cost ($US)	Prevalence
Regimen	55	7.23%
Medical visit	84	
X-Ray	20	
Total cost per OI patient	159	
Average Cost per ARV patient	**12**	

Infrastructure

The infrastructure component includes the estimated capital costs for scaled-up facilities and new buildings and equipment. Such investment will be needed to accommodate an average of close to 20,000 new patients added to the *Masa* Programme annually (as described previously). Per recent *Masa* Programme data, we calculated that each existing clinic currently provides ongoing care to an average of 385 patients annually. After discussions with clinicians and administrators in Botswana, we believe that most clinics are currently operating under their capacity. Our model estimates, therefore, that new and scaled-up clinics can increase capacity from an average of 385 to an average of 600 patients per clinic annually.

To accommodate the outpatient care that will be needed by the additional patients added to the *Masa* Programme annually, we estimate that infrastructure resources needed is equivalent to 40 new clinics that could operate at a capacity of 600 ARV patients per year. The estimated cost of one outpatient clinic was calculated by assuming an average of 200sq. meters per clinic at a cost of $100 per sq. meter. This sq. meter price estimate is based off of recent clinic construction costs provided by the Ministry of Health. An additional $5,000 was added for new equipment, bringing each total clinic cost to $25,000. The total new outpatient clinic infrastructure investment needed annually is therefore approximately $1,000,000.

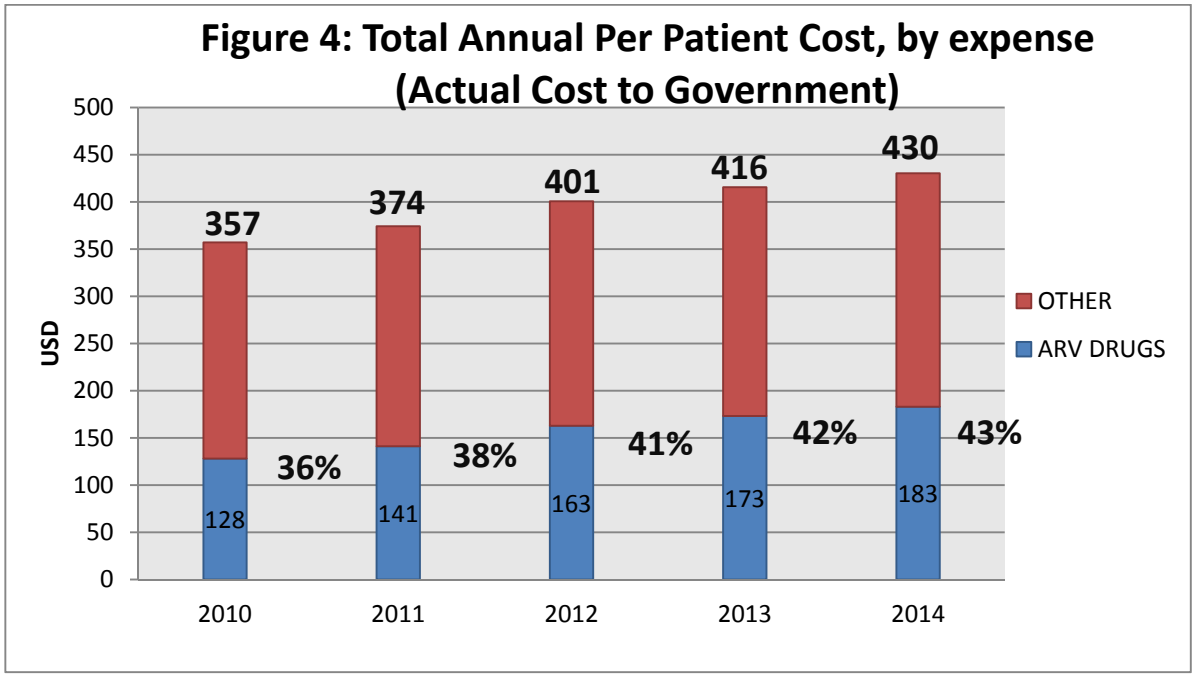
Even though HIV treatment creates more of an outpatient clinical demand, the capacity of inpatient care may also need to be increased as well. An average of 100 hospital beds may need to be added annually. The estimated cost per additional patient bed is approximately $100,000

[9] Average cost per ARV patient is the Total cost per OI patient multiplied by the prevalence

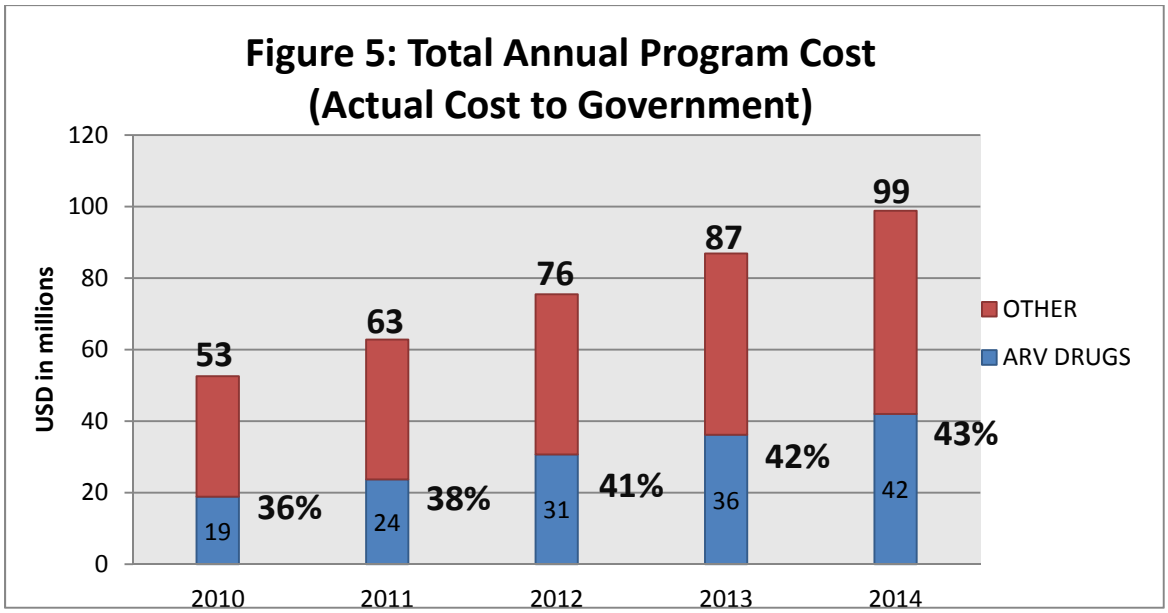
which brings the total inpatient capacity expansion to around $1,000,000 annually. Averaging out the total infrastructure investment per ARV patient comes out to $16 dollars per patient annually.

Final Projections

To calculate the first of the two final outputs (*Masa* ARV per patient treatment cost projections 2010-2014), we summed each of the cost inputs for years 2010-2014 (which were distributed over total number of *Masa* enrollees). Figure 4 below depicts the results of the cost per *Masa* patient broken down by year. The more substantial jump from 2009 to 2010 and then from 2010 to 2011 is because of the projected shift in number of patients on Truvada as well as the incremental inclusion of the cost of efavirenz (as discussed previously).The estimated per patient cost per year is depicted in Figure 4.



To calculate the second final output, (Total *Masa* ARV Cost, 2010-2014) we multiplied the total per person cost of HIV per year (as seen in Figure 4) by the number of *Masa* enrollees. The results are illustrated in Figure 5.



Assumptions and Limitations

As with any modeling or projection work, there are a number of assumptions and limitations in our costing model. A brief description of each follows.

As mentioned above, we assume an average enrollment of 1,600 patients monthly to remain constant through 2014. Implicit in our model is that current facilities are not operating at their full capacity. We calculated the average number of current patients in the clinics for each district. We then added accordingly in order to reflect scaling-up existing facilities. The average number of patients, country-wide, per clinic was 385 (median 295). These calculations did not take into account the number of patients seen by hospitals. We therefore allowed for a 56% increase in this average capacity, and used an estimate of 600 patients per clinic.

These calculations were done using data from the Ministry of Health (HAART Patient by sites, waiting list and outsourced, July 2009). Inflation and discount rates are not factored in.

It is worth noting that this model does not incorporate the partial costs, covered by the *Masa* Programme, associated with patients that have been outsourced to the private sector.

We presume that resource management will improve drastically over time. This improvement is implied in the previous assumption as each clinic will have to manage its resources more efficiently in order to accommodate an increase in the number of patients seen per day. It is again implied in the assumption that clinics are not currently operating at their full capacity.

An important factor to mention is the number of patients already eligible for ART are not 100% enrolled in the *Masa* Programme, and any potential changes in the eligibility criteria have not been taken into account.

Another assumption made was that the pharmaceutical drug costs factored into these projections will not change between 2009 and 2014. We had to hold this assumption true because we would have had to conduct an extensive pharmaceutical drug market analysis in order to predict how the prices might change in five years. Along with this supposition, we also did not account for the introduction of possible generic drug alternatives.

We have assumed over the next five years that the current regimen protocols in Botswana will not change. This means that all new patients enrolled will be put on Truvada+NNRTI for first line. Those needing to switch from Combivir+NNRTI as a result of Combivir-related toxicity will be put on Truvada+LPV/r. We have not incorporated any costs associated with potential Combivir-related toxicities.

Lastly, these projections do not include any medical personnel related training costs related to training new staff or providing refresher courses in providing ART. It is safe to assume that a certain level of training costs will be incurred on an ongoing basis.

Conclusions

The costing exercise we conducted highlights that the three primary drivers of the provision of ART in *Masa* are ART drugs, laboratory tests, and personnel. In order to achieve full coverage of eligible patients over the next five years, the enrollment rate must dramatically increase, which requires significant investment in scale-up efforts.

We hope that these findings will allow Botswana policymakers to allocate the resources needed to continue providing ART to current patients in *Masa*, as well as allow for the scale-up necessary to cover all Batswana needing treatment in the years to come.

MOC CLINICAL COHORTS

The MOC Clinical Cohorts have provided information on both their own clinical objectives, and on clinical outcome and cost data needed to complete the Costing estimates presented above.

Bomolemo Cohort

A Pilot Study Evaluating the Efficacy and Tolerability of Tenofovir and Emtricitabine (Truvada) as the Nucleoside Reverse Transcriptase Inhibitor (NRT) Backbone as First-Line HAART for Adults in Botswana ('Bomolemo'),

The use of combination, highly active antiretroviral therapy (HAART) since the mid-1990s has resulted in significant and sustained reductions in morbidity and mortality from HIV infection, including significant declines in HIV-associated nephropathy (HIVAN).[10] At the same time, however, a variety of HAART-related renal side effects have been noted, including proteinuria and renal tubular damage, interstitial nephritis, nephrolithiasis, and overall declines in glomerular filtration rate (GFR).[11] Kidney function has been estimated to be abnormal in up to 30% of HIV-infected patients.[12] In addition, other metabolic complications such as type 2 diabetes and hypertension may also contribute to renal dysfunction over time. The nucleotide analogue tenofovir has become a prominent component of combination antiretroviral therapy due to its tolerability, convenient dosing, and potency when used with two other active antiretroviral agents, yet concerns regarding its renal tubular toxicity remain. While several case reports and cohort studies have noted varying degrees of tenofovir-associated renal tubular dysfunction or small declines in GFR[13], there has been little characterization of renal function overall within large HIV-infected cohorts.

Currently over 150 thousand persons in Botswana have been diagnosed with HIV/AIDS and can be expected to receive antiretroviral therapy at some point during the course of their disease. Given the current guidelines, all the patients who start their treatment or experience treatment

[10] Lucas GM, Eustace JA, Sozio S et al. Highly active antiretroviral therapy and the incidence of HIV-1-associated nephropathy and response to highly active antiretroviral therapy. Lancet 1998; 352: 783–784.
[11] Ro¨ ling J, Schmid H, Fischereder M et al. HIV-associated renal diseases and highly active antiretroviral therapy-induced nephropathy. Clin Infect Dis 2006; 42: 1488–1495.
[12] Gupta SK, Eustace JA, Winston JA et al. Guidelines for the management of chronic kidney disease in HIV-infected patients: recommendations of the HIV Medicine Association of the Infectious Diseases Society of America. Clin Infect Dis 2005; 40: 1559–1585.
[13] Jones R, Stebbing J, Nelson M et al. Renal dysfunction with tenofovir disoproxil fumarate-containing highly active
antiretroviral therapy regimens is not observed more frequently: a cohort and case-control study. J Acquir Immune Defic 2004; 37: 1489–1495.

failure will have Truvada in their regimen. Consequently, treatment guidelines have been developed for the screening and management of chronic kidney disease in HIV-infected persons. Recommendations include routine urinalysis for proteinuria and calculated creatinine clearance or eGFR, as well as careful attention to co morbidities that may contribute to elevated risk of kidney disease. In order to gain better understanding of the prevalence and risk factors for renal dysfunction among HIV-infected patients, the Bomolemo study evaluated 309 HIV-infected participants to (1) describe the overall prevalence of varying degrees of reduced eGFR within this population; (2) determine risk factors for reduced eGFR and chronic kidney disease; and (3) compare the prevalence of reduced eGFR and its associated risk factors within the cohort matched for age, gender, and other individual factors .

Data

In this study 309 HIV-infected persons were followed on average 58.8 weeks (median 72 weeks), 37% were men, and the mean age was 36.9 years. During the course of the study, six patients passed away. Mean creatinine level was 63.6 µmol/L (normal range of creatinine 35-100 µmol/L)

Table 8: Baseline descriptive statistics (Bomolemo)

Stats	N	mean	median	Sta. Dev.	min	max
Creatinine	294	63.6	59	30.7	30.0	397
CD4	303	162	166	93	2	471
BMI	288	22.8	22	5.8	14.0	62
Age	309	36.9	36	8.3	20.0	66
Male	309	0.37	0	0.48	0	1
Death	6	0.02	0	0.14	0	1
Log viral load	306	5.03	5.11	0.69	2.60	5.88
Weeks on study	309	58.8	72	24.7	0	87

Average creatinine level during the study for each participant varied between 36 and 383 µmol/L. “Creatinine level within” varied between -231 and 959 µmol/L, which is not to say that any participant actually had negative creatinine level. The within number refers to the deviation from each individual’s average over time and, naturally, some of those deviations must be negative. Then the negative value is not disturbing, but the positive value is. Did some participants really deviate from their average by +959 µmol/L? In our definition of within, we add the global average of 68 µmol/L. Some participants did deviate from their average by 959-68 = 892 µmol/L, which is still large.

The reported standard deviations are surprising. They show that the variation in creatinine across participants is nearly half of that observed within a single participant over time. That is, if we were to draw two participants randomly from our data, the difference in creatinine level is

expected to be nearly half of the difference for the same participant in two randomly selected visits.

Data analysis

The analyses were all conducted using the statistical software package STATA 11.0. Creatinine level above 100μmol/L and viral load above detection level were treated as dichotomous variables, which can take the following values: "toxic level", which represents creatinine above 100 μmol/L, and "low viral load," meaning below detection level.

The association between renal toxicity and treatment were investigated in a series of logistic regression models. To take into account the potential clustering of our data (since participants were observed over time), we carried out a random effect autoregressive logistic model in STATA using the xtlogit command.[14] We employed Gauss-Hermite quadrature to evaluate and maximize the marginal log likelihood. We used the adaptive quadrature method as described by Rabe-Hesketh & Skrondal (2008). Initially, crude odds ratios were calculated. Then we adjusted for the treatment and individual variables. Analyses were conducted separately for renal toxicity, general toxicity, renal failure, and death.

Results

Table 9 reports the results of a longitudinal logistic regression to investigate the probability of renal toxicity based on treatment and individual characteristics. In this study, the creatinine level in six patients passed the 100 μmol/L threshold. All the participants received a combination of the following drugs: abacavir, Alluvia, Combivir, didanosine, efavirenz, Lamivudine, nevirapine, Truvada, and zidovudine. We did not find any significant effect of any medication on renal toxicity except for Truvada. The results indicate that for the patients on Truvada, surprisingly, we see about a 76% decrease in the odds of developing renal toxicity. The main reason is that almost everybody on the study is taking Truvada. The odds of renal toxicity are four times higher among the male participants. Higher body mass index also lower the odds of renal insufficiency. As for the time variable, we used a quadratic function. Our analysis shows that the likelihood of developing toxicity reaches its maximum at 66 weeks after initiation of treatment.

[14] Rabe-Hesketh S, Skrondal A:*Multilevel and longitudinal modelling using Stata.* College Station, TX: Stata Press; 2008.

Table 9: Logistic analysis of longitudinal data

Toxicity	Odds Ratio	Std. Err.	z	P>z	[95% Conf.	Interval]
Truvada	0.24	0.10	-3.61	0	0.11	0.52
Aluvia	2.77	2.55	1.1	0.27	0.45	16.87
Low viral load	0.71	0.23	-1.07	0.285	0.37	1.33
Male	4.13	2.25	2.6	0.009	1.42	12.00
BMI	0.70	0.06	-4.36	0.000	0.60	0.82
Duration (weeks)	0.88	0.05	-2.22	0.026	0.78	0.98
Duration square	1.00	0.00	1.4	0.163	1.00	1.00
Number of observations = 2826 Number of individuals = 289						
Number of observations per individual: min = 3 avg = 9.8 max = 19						

Note: What we found in this analysis is inconclusive, since almost everybody is taking Truvada. Therefore, we are repeating this analysis using different methods and will report these results separately.

Botsogo Cohort

CD4 trajectories Over Time among ART Naïve Patients in Botswana

Introduction

The invention and spread of anti-retroviral treatment (ART) has helped reduce the prevalence of AIDS all over the world. From the many clinical trials and observational studies, the efficacy of ART has been proven. However, it accompanies toxicity, tolerance, and financial problems. So, researchers are now focusing on when to start treatment. For the decision of initiation of treatment, although AIDS defining events and opportunistic events are also considered, CD4 cell count per mm^3 is used frequently. The criteria vary by countries. In some African countries, the cutoff point for eligibility is 200 or 250 CD4 cell count. On the other hand, some developed countries used 500 CD4 count as the initiation of the treatment. In Botswana, the criteria used to be 200, but it was changed to 250 in 2008. Since a lower CD4 means a higher chance of developing AIDS, it is better clinically for a patient to have a higher CD4 count. However, once a person becomes HIV-positive, generally, CD4 counts go down without treatment. So, we need to find out the patterns of CD4 cell count changes over time for treatment naïve patients, such as the rate of decrease. Thus, we will examine the CD4 trajectories over time and find important factors which influence the decrease of CD4 count among ART naïve patients in Botswana.

Dataset

The 'Botsogo' study is the natural history study, an observational prospective study to gather data on HIV disease progression from infected individuals who do not qualify for the Botswana ART Program. This study is still on-going. One of the main objectives is to estimate the rate of CD4 cell decline among ART naïve individuals. The endpoints are the first AIDS defining illness, CD4 cell count < 200 (which means move to Botswana ART program), 12 months follow up after the last participant is enrolled, or death. Since this study started in 2005, the criteria of CD4 count for initiation of treatment is 200. This was changed during the study to 250. The inclusion criteria are HIV-positive adults whose CD4 cell count of ≥ 400 cells/mm^3 at least 90 days prior to the study entry. Participants visited clinics every 3 months including 1 month after enrollment.

In this study, 455 individuals enrolled initially. As we can expect, the number of people in the study is getting smaller as time goes on. The longest follow-up time is 63 months. However, because the number of people who remained so long on the study was small, we focused on the first three years of follow-up (until 36 months). CD4 category, RNA category, BMI category, gender, age, and anemia status are considered as baseline covariates. Among those baseline covariates, baseline CD4 and RNA category are of interest mainly. The majority of this cohort is women (81%). Since most patients have higher CD4 when they enrolled the study, 43% of

patients are in the highest baseline CD4 group (> 500 cells/mm^3). For the RNA category, 60% of participants have over 5,000 copies, or viral load, at enrollment. This might be because every participant is HIV-positive and ART naïve. We can generally think that if a person has higher CD4 count, which is a good situation, we can expect lower viral load for that person. However, in our analysis, it seems like many people are in the highest CD4 group and highest RNA group. In this analysis only 20% of people have > 30,000 RNA copies in the highest CD4 category (> 500 cell count), whereas 48% of people have > 30,000 RNA in the lowest CD4 category (< 350 cell count). Using these criteria, only one person has undetectable RNA which means < 400 RNA copies in the lowest CD4 group (< 350 cell count), but 19 percent of people show undetectable RNA in the highest CD4 group.

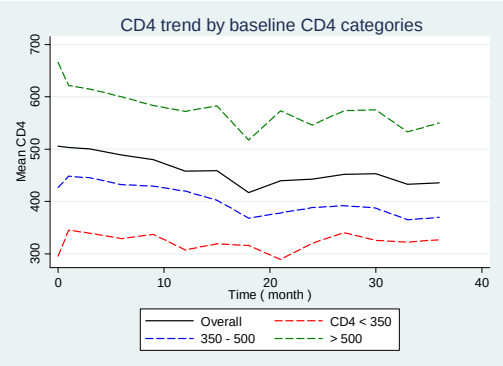
Method

Figure 6 includes two graphs which can explain the trend of CD4 individually and averagely. From Figure 6.a and 6.b, we can find the CD4 trend over time on the average sense. Based on the mean CD4 at each visit (month) by baseline CD4, as we can expect, the mean CD4 of the highest baseline group keeps the first line. The interesting point is the sharper drop of CD4 in the highest CD4 group (> 500 cell count) than in lowest CD4 group (< 350 cell count). Figure 6.b is the same graph as Figure 6.a except RNA categories are considered as strata. Undetectable RNA group (RNA< 400 copies) shows large mean CD4 and the severe risk set (RNA > 30,000 copies) has low mean CD4 over time. It seems that the pattern of severe group based on RNA (> 30,000 copies) is different from other groups. Thus we can consider time by CD4 or RNA interaction as covariates. To justify that the mixed effect model with random intercept is reasonable, we fitted two models: (1)mixed effect model with random intercepts only, (2)both random intercepts and slopes; then compared goodness of fit based on AIC. Baseline CD4 category, time, and CD4 category by time interaction are included. The AIC of the random intercepts only model is -6409.9 and the AIC of the random intercepts and slopes model is -6011.6. Since the random intercepts only model has smaller AIC, we can say that the random intercepts model gives better fit in this data. From now on, random intercept only model is considered.

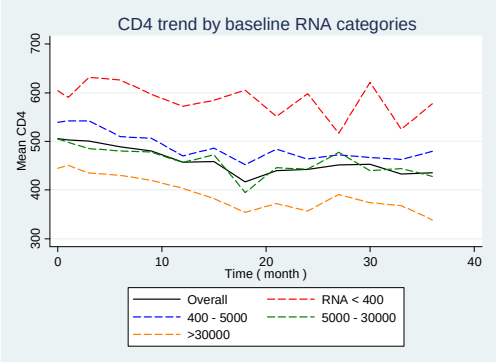
For the model selection, baseline CD4 and RNA category, time, and interaction terms are included in the model first. Based on AIC, the best model has quadratic effect of time and interaction between time by CD4 category, RNA category, and quadratic time by CD4 category interaction. However, when we fitted this model, the coefficients for $time^2$ by CD4 category are very close to 0 and it is hard to interpret this interaction; hence, exclusion of this interaction from the model. Most fixed effects are significant. From type three tests of fixed effects table, RNA category has p-value above 0.05, but this is marginally significant. Except RNA category, other factors are very significant. The estimated correlation is 0.5102, variance for random intercept is 0.01005, and within subject variability is 0.009646.

Figure 6: Basic Graphs for Observing CD4 Trend

(a) Mean CD4 over time by baseline CD4 categories



(b) Mean CD4 over time by baseline RNA categories



Discussion

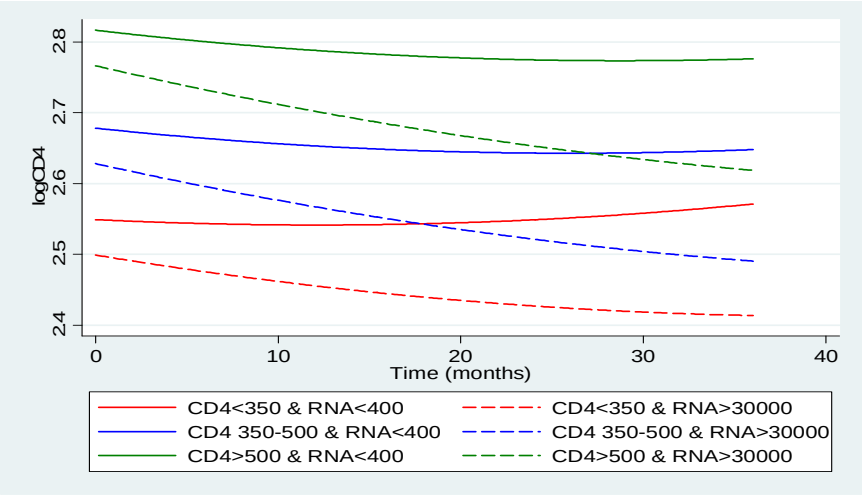
Since our model includes quadratic effect of time and time by CD4 and RNA category interactions, it is difficult to see the relationship directly between baseline CD4 and RNA category and CD4 observations over time. There are several combinations of CD4 and RNA categories, however, we compare two extreme cases; baseline RNA<400 copies vs. baseline RNA>30000 copies. For example, a person who has RNA<400 copies and CD4<350 cell count at the baseline will decrease CD4 0.3% after 1 month and decrease 1.7% after 1 year. We can see the trend that in each RNA group, the decrease rate is going up as the time interval gets larger. Also, the rate of decline increases as baseline CD4 is higher which we expected from CD4 trend graphs. That is, CD4 decreases sharply when it starts above 500 cell count and the decrease rate is not linear. If we compare between two RNA groups, RNA>30,000 copies group, which means severe risk set, has a higher decrease rate than RNA<400 copies group. So, we could conclude that CD4 decreases with high rate when patients have higher RNA.

The interesting point is that the trend turns upward at some time point in RNA<400 copies group which is an unexpected situation (Figure 7). This pattern is only observed in RNA<400 copies group. It seems that a small number of patients in that group (55) can explain the unexpected situation.

Conclusion

In summary, CD4 count has different patterns by baseline CD4 and RNA category over time. It seems time affects CD4 count nonlinearly. We found baseline RNA is a good predictor of rate of disease progression. Therefore, by considering these patterns of CD4 over time, the composite criteria of CD4 and RNA for treatment initiation need to be considered in Botswana.

Figure 7: Fitted Model



The Kgatelopele Study

The Kgatelopele Study, *Long-Term HAART Study*, was an observational study to assess the long-term outcomes of antiretroviral therapy in Botswana. This observational study was supposed to collect long-term HAART outcome data of HIV-infected adults previously enrolled in the original three-year Adult Antiretroviral Treatment and Drug Resistance "Tshepo" Study, which were transferred to the national program after the end of the study. This data was important as it would enable a long-term outlook on the well-being of patients on the current first-line Truvada regimen.

This part of the study relied heavily on the data which was collected by the national programme. The data that was able to be compiled was not enough to complete the goals of this study completely. However, using the data from Tshepo study, we managed to do some intended analyses, of which the abstracts are included in this report. Both the long-term outcomes and the complications of HAART remain important areas of further study for the country and region.

ABSTRACTS PREPARED TO DATE

Nine Year Outcomes from the Botswana National HIV/AIDS Treatment Program: 2002-2010

Background: Botswana is one of the first sub-Saharan African countries to have a national antiretroviral treatment (ART) program and, thereby, able to report on long-term outcomes.

Methods: The analysis was done on only 102,713 patients, who started treatment through the national program from 2002 to 2010. Logistic regression analysis was performed, using Stata. Rates of mortality, loss-to-follow-up, and CD4+ cell count changes were evaluated from treatment initiation.

Results: Of the patients included in analysis, the median age was 36 years old (IQR 31-43), 62% were women, and median baseline CD4+ cell count was 151(cells/µl) (IQR 85-201). Of patients initiated on treatment, 5,257 deaths were recorded. Mortality, highest in the first three months after treatment initiation (143.05 per 1,000 p-y), dropped to 14.2 per 1000 p-y in the second year, and steadily decreased to 1.5 in year 7. Proportion of patients who died in the first year of treatment dropped from 20% [504 deaths out of 2,807 patients] in 2003 to 3% [426 deaths out of 12,575 patients] in 2009. For each subsequent year of treatment initiation, median CD4+ cell counts increased, and mortality rates decreased. Strongest risk factors for death were switching medication, baseline CD4+ cell count, and being male. Odds of survival increased in each year of the program. No advantages in terms of mortality either between efavirenz and nevirapine, or between zidovudine and tenofovir (first line treatment as of 2008) were seen.

Conclusion: The Botswana National HIV/AIDS Treatment Program reduced mortality among adults infected with HIV in Botswana similar to rates seen in other countries, but with much longer observed time and bigger sample size than any other reported national program. As the life of the program increased, the odds of patients' survival improved. Patients on tenofovir do not seem to have different survival rates than those on Combivir.

Variation in mortality rates 2002-2010, Review of the Botswana National HIV/AIDS Treatment [Masa] program data.

Objective: To examine the variation in mortality rate among HIV infected individuals in Botswana by district.

Methods: Of the data analyzed, 102,713 patients received ART treatment through the Botswana National HIV/AIDS Treatment Program across health districts from 2002 to 2010. A multilevel analysis was conducted, using Stata. Rates of mortality, and CD4+ cell count changes were evaluated by district over time.

Results: The largest health district in terms of the number in the database is Gaborone (17,608 patients) and the smallest is Mabutsane (159 patients). About 60% of the patients were female across all districts. The mean age at treatment initiation in different districts was quite similar (lowest 36, highest 38). Shortest mean pretreatment follow-up time was in Selibe-Phikwe (96 days) and the longest was Okavango (978 days). For the post-treatment initiation follow-up, Mabutsane has the least number of days (90) and Gaborone the most (1,487). Mortality rates in the districts ranged from the lowest 1.22% (17 deaths out of 1,393 patients), to the highest 15.3% (351 deaths out of 2,294 patients). In the regression analysis mortality rates were statistically significantly higher in districts comparing to Gaborone (the capital), controlling for sex, age, baseline CD4 cell count, duration of pre- and post-treatment initiation follow-up time, year of initiation, first-line medication (NRTI and NNRTI), and if they switched medication.

Conclusion: Botswana national ART program has successfully reduced mortality among HIV infected patients. We found a statistically significant variation in mortality among districts. Further research needs to investigate factors that can potentially cause this variation.

Costing the National Antiretroviral Therapy Program in Botswana

Background: The Botswana government has demonstrated clear and solid commitment to providing antiretroviral treatment (ART) to people living with HIV/AIDS. Public health expenditure increased from 5 percent of GDP in 1999, to 7.2 percent of GDP in 2006. Some of this increase is due to the national HIV/AIDS treatment program, *Masa*. The *Masa* Programme currently provides ART to more than 110,000 people living with AIDS in the country.

Objective: The objective of the costing exercise was to estimate the cost of continuing to provide, and expand, ART in the public sector in Botswana through the year 2014. The findings will allow program planners and policymakers to look at the total program cost and human resource requirements of providing and scaling-up ART in the public sector.

Method: We developed demographic and epidemiologic models for the HIV+ population and its distribution by age and gender. Our demographic and epidemiologic data was collected from a number of sources including: resources from the Ministry of Health and Central Statistics Office, statistical databases compiled by the UN Population Division, the World Bank, UNICEF, and the 2008 Botswana AIDS Impact Survey. To project the cost of the *Masa* Programme through 2014, we focused on the principal cost drivers in *Masa* by including the costs from the following major categories: ART drugs, laboratory tests, human resources, opportunistic infections diagnosis and treatment, and infrastructure. These cost inputs were adjusted for changes over this time period. The expected increase in patient enrollment in *Masa* through 2014 was also estimated. Additionally, we developed different scenarios allowing for changes in potential medication prices and donation levels.

Findings: In 2009, more than 105,000 people were receiving their ART through public sector. We estimate this number will increase to 180,000 in 2014 if the treatment eligibility changes (from CD4 cell count 250 cells/ml to 350 cells/ml) and if more than 40% of the untested population is tested. Our model suggests that in 2009 the average per patient costs was 513 USD, which we suggest will increase to 664 USD per patient per year in 2014. Due to the current drug donation agreement in Botswana, in 2009 the government paid 387 USD per patient on ART. We project this will increase to 495 USD per patient in 2014 due to the growing number of patients expected to be on the new "first line" ART regimen. The estimated total cost of *Masa* amounted to 56 million USD in 2009, and we project, with certain assumptions, that this figure may reach 134 million USD in 2014.

Conclusion: This costing exercise highlights that the three primary drivers of the provision of ART in *Masa* are ART drugs, laboratory tests, and human resources. Further investment in scale-up will be needed to achieve full coverage of eligible patients over the next five years.

Clinical and Immunologic Progression in People Living with HIV with High CD4 Counts in Botswana

Objective: To examine factors associated with clinical and immunologic HIV disease progression in a cohort of people living HIV in Botswana.

Design: Analysis of data from a prospective, longitudinal study of HIV-infected people, followed every 6 months for 5 years in Gaborone, Botswana.

Participants: We enrolled 455 HIV-infected persons with CD4 cell counts above 450 cells/mL, who were not clinically eligible for antiretroviral treatment (ART) at time of entry into the study.

Measurements: Structured clinical interviews; protocol-directed physical examinations; CD4 lymphocyte counts; plasma HIV RNA.

Results: There were 370 women and 85 men in this study. Median baseline CD4 cell count was 468 cells/mL (IQR 381 – 595); median baseline RNA 13,000 copies/mL (IQR 2650 – 47,800). Baseline CD4 count and viral load were the strongest predictor of subsequent clinical progression. Age, gender, anemia, BMI, and other infections were not associated with progression. Among the participants with CD4 counts >500 cells/mm^3 at baseline, those with higher viral loads were more likely to progress to AIDS. By the end of the study, only 101 (22%) of the participants were on ART, with a median time to eligibility of 51 months.

Conclusions: We found that CD4 cell counts declines faster for the patient with CD4 counts above 500 cells/mL than those below 500 cell count. Viral load can be an important factor in determining disease progression.

A Randomized Clinical Trial of Protease-Inhibitor-Sparing cART among HIV-1C Infected Adults Receiving First-Line Combination Antiretroviral Therapy in Botswana: Longitudinal Modeling of Three-Year Gains in CD4 Count

Background: National initiatives offering protease-inhibitor-sparing ART have commenced in sub-Saharan Africa. The Tshepo study is an RCT evaluating the long-term efficacy and tolerability of one combination NRTI and one NNRTI among adults in Botswana.

Methods: Completed, open-label, randomized study of 433 ART-naïve adults followed for 3 years, using a 2x2 factorial design comparing efficacy and tolerability among: ZDV/3TC vs. d4T/3TC (NRTIs) and EFV vs. NVP (NNRTIs). Our focus is on modeling CD4 counts measured at baseline and every two months after treatment initiation. We fit a stochastic mixed model with a knot at 3 months to account for the acute effect of treatment on CD4 count increase and the more gradual increase thereafter

Results: 293 females (68%), 140 males; median age 33.5 years, median baseline CD4 count 200 [IQR 135-250], and median follow-up 2.99 years [IQR 2.76-3.00]. Treatment group and gender were significant predictors of rate of CD4 increase. According to the model, CD4 counts rose by an average of 125 cells during the first 3 months on cART regardless of treatment assignment or gender. Differences emerged thereafter. Specifically, the model-predicted rise in CD4 count from 3 months to 3 years after treatment initiation for women was 137 cells for ZDV/3TC/NVP; 189 for ZDV/3TC/EFV; 181 for D4T/3TC/NVP; 235 for D4T/3TC/EFV; for men, 103 cells for ZDV/3TC/NVP; 152 for ZDV/3TC/EFV; 144 for D4T/3TC/NVP; 197 for D4T/3TC/EFV.

Conclusions: Interestingly, the optimal first-line regimen for CD4 increase in this study was d4T/3TC/EFV, a regimen that is no longer recommended because of the toxicity related to d4T. Women had higher CD4 gains than men.

When should antiretroviral treatments be started in Botswana? Survival Model and Propensity Score Model

Background: The question of when to start antiretroviral therapy (ART) for infection with HIV has been much discussed, and treatment management guidelines have oscillated from the "hit hard, hit early" philosophy to conservative approaches of deferring treatment in asymptomatic patients until CD4 cell counts are 200 cells/L , despite there being little data on the subject. In this study, results from an analysis of Tshepo, a randomized trial, are presented that provide some insight into this question.

Method: We used part of the dataset from Tshepo with 434 observations with 24 death events (5.53%). They are randomized to 4 treatment arms;
ZDV/3TC/NVP; ZDV/3TC/EFV; D4T/3TC/NVP; D4T/3TC/EFV.
To find the effect of baseline features, we conducted survival analysis with outcome of time to death. We use Kaplan-Meier estimate and Cox proportional hazard model.

Results: The range of baseline CD4 is 2 to 349 with median CD4 counts of 199. We made two groups (less than 200 CD4 cell count and 200-350 CD4 cell count) using the threshold in the 2005 Botswana guidelines; CD4 counts of 200 we can observe significant difference between two groups; <200, 200-350 from logrank test (P = 0.0448). The group defined as CD4 count less than 200 shows lower survival than CD4 count 200 to 350. From the Cox proportional hazard model, we found four key baseline characteristics; CD4 count, BMI, anemia, and Karnofsky Score. Karnofsky Score represents disability level; as the score is lower, the person has worse functional impairment. As patients have lower CD4 counts, higher BMI, lower disability level, and anemia at the baseline, the hazard to death increases. Especially, the hazard ratio is 3.29 (95% CI: 1.052 – 10.257) for patients with anemia versus without anemia at the baseline.

Conclusion: Treatment should be started early to prevent AIDS and death. However, there are several concerns such as toxicity and adherence rate. From our analysis, it is beneficial to start the treatments at high CD4 cell counts, when disability level is lower.

Treatment-modifying toxicity and mortality among HIV positive patients in Botswana

Background: The greater availability of combination-antiretroviral therapy has significantly curbed AIDS-related mortality in resource-poor nations. However, due to the unavailability of ART with fewer side-effects and insufficient monitoring, the scaling up of ART may have resulted in increased mortality due to treatment-modifying toxicity. Few studies have evaluated the impact of ART-related toxicities on mortality in developing countries.

Study design: The Tshepo trial consisted of 650 HIV-positive cART-naïve adults with baseline CD4 counts <350 cells/ml, attending ART treatment/screening clinics in Gaborone, Botswana. Participants were randomized to three nucleoside reverse transcriptase regimens (zidovudine/lamivudine, zidovudine/didanosine, and lamivudine/stavudine) and two non-nucleoside reverse transcriptase inhibitors (efavirenz vs. nevirapine), and were followed for approximately three years. Treatment-modifying toxicities included grade three or higher symptoms, laboratory abnormalities, and diagnoses.

Statistical Method: We used Cox Proportional Hazard regression to evaluate the impact of treatment on development of toxicity, and the impact of treatment-modifying toxicity on non-accident-related mortality.

Results: Ninety participants developed treatment-modifying toxicity, and there were 34 non-accident-related deaths. Six deaths (18%) were potentially due to direct effects of treatment toxicity. The stavudine/lamivudine NRTI regimen had 1.94 (1.11, 3.36) times the risk of toxicity compared to zidovudine/lamivudine, while efavirenz had a 0.6 (0.39, 0.94) times the risk compared to nevirapine. Treatment-modifying toxicity increased the hazard of non-accidental death 12.79 (3.86, 42.34) times.

Conclusion: Treatment toxicity was a strong predictor of mortality in this cohort. We recommend better monitoring of patients on ART for earlier detection of life-threatening adverse events, and close clinical monitoring of patients who develop treatment-modifying toxicities.

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