Title: Corrections of Research Report: Descriptive Study of Surrogate and Clinical Outcomes of Antiretroviral treatment in Selebi Phikwe, Botswana from June 2004 to June 2005

Key: Changes are reflected in bold.

Presentation:

1) Grammar and spellings: A robust spelling and grammar editing has been done. However, there could still a few grammar and spelling mistakes that escaped the eye
2) The investigator team is referred in third person
3) Each Chapter is introduced

Literature Review

1) Role of Trials in the evolution of ART has been stated on page 4:

   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.

2) More information on Monotherapy has been included on page 4:

   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).

3) More information has been included on how HAART came about on page 5

4.13 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).

4) Provisos for a successful ART program are included on page 6

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.

5) Definitions of outcomes are included on page 8

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).

6) Clinical outcomes strengthened on page 8

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).

7) Additions to Laboratory outcomes on page 9

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)**

8) Additions to adherence on 10 Page:

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).

Chapter 2: Introduction to Methods and Materials

1) **Introduction to Chapter 2 is inserted on page 12**

   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) **Sub-points 2.4 and 2.5 are merged in 2.3 on page on page 13**
3) **Population size included on page 15**

   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
   4) Information on data processing, including coding included on page 18
   2.9 Data Processing
   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.

5) All the tables have been redone to include percentages from pages 22-28

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%)**

Discussion

1) Proportion of individuals put on ART against target is described on page 29

   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.**

2) Effects of HIV on productive age group described on page 29

   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.

Chapter 5

1. Conclusion added on page 34

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.