A REVIEW OF THE ROUTINE MONITORING DATA FOR ANTIRETROVIRAL PATIENTS IN THE PUBLIC HEALTH SECTOR IN THE WESTERN CAPE PROVINCE, SOUTH AFRICA

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Declaration

I, Dr Peter Alwin Bock, hereby declare that the work on this dissertation is based on my original research and has not, in whole or in part, been submitted towards another degree, at this university or elsewhere. The university is empowered to reproduce either the whole or any portion of the contents for the purposes of research.

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Abbreviations

3TC	Lamivudine
ART	Triple antiretroviral regimen
ARV	Antiretroviral
AZT	Zidovudine
CD50prop	Proportion of patients with a baseine CD4 count < 50 cells/mm3
CHC	Community Health Centre / Day Hospital
D4T	Stavudine
DALY's	Disability adjusted life years
DOH	Department of Health
DTF	Desmond Tutu Foundation
EFV	Efavirenz
HIV	Human Immunodeficiency
IRR	Incidence rate ratio
LTF	Lost to follow up
M&E	Monitoring and evaluation
MRC	Medical Research Council
MSF	Médecins Sans Frontières
NDOH	National Department of Health
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OIs	Opportunistic infections
PCR	DNA HIV Polymerase chain reaction test
PGWC	Provincial Government of the Western Cape
PHC	Primary Health Care
PMTCT	Prevention of mother to child transmission
TB	Tuberculosis
TFI	Transfer in
TFO	Transfer out
UCT	University of Cape Town
UNAIDS	United Nations AIDS council
VCT	Voluntary counselling and testing
VL	Viral Load
WC	Western Cape
WHO	World Health Organization
YLL	Years life lost

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Executive Summary

Introduction

The first patients started on antiretroviral therapy (ART) in the Western Cape Province public health service began treatment as early as January 2001. These patients were funded jointly by non-government sources, such as the Desmond Tutu Foundation (DTF) and Médecins Sans Frontières (MSF), and the state, on account of the then limited availability of government funding for ART. The government funded rollout of ART in South Africa began in April 2004. Concerns about poor adherence and viral resistance led to a nationwide emphasis on the development of a good monitoring system for ART. The Provincial Government of the Western Cape (PGWC) has, in conjunction with the World Health Organization (WHO), developed a monitoring system to provide quarterly outcome data for patients on ART.

Aims and Objectives

This study aims to describe and describe and analyse routine data produced on defined clinical and immunological outcomes of patients on ART by the monitoring system, thus assessing the feasibility of an ART programme in the public health sector in the Western Cape Province.

Methods

This study reviewed patient information captured in both the paper based monitoring system and electronic databases. Data on all patients started on ART since January 2001 until June 2005 was included in the study. The

monitoring system, developed by the WHO, uses paper-based ART registers at clinics to capture relevant patient information. All patients less than 15 years of age were classified as children. The baseline data recorded in the monitoring system is limited to the percentage of children with a baseline CD4 percentage < 15% and the percentage of children who were treatment-experienced.

Results

A. Adults

The total number of adults on ART increased from 81 in 2001 to 9724 in July 2005. The monitoring system captured data for 8698 adult patients started on treatment during this period, which is 97.5% of the total number of adults enrolled. 3.6% of these patients were treatment experienced and excluded from further analysis.

Outcome data showed that 93.6%, 90.1%, 84.5%, 81.7% and 82.9% of patients were still in care at 3, 6, 12, 24, and 36 months respectively. The cumulative death rates for adults on treatment at these monthly intervals was 4.4%, 6.1%, 8.2%, 15.6%, and 14.2% respectively. The percentage of patients on second line treatment remained low at 1.2% at 12months and 3.4% at 24 months. Viral load suppression rates remained between 87% and 91% for cohorts of adults on ART for up to 36 months.

The number of adult patients started on ART from 2001 to 2004 was 81, 255, 576, and 4167 per year respectively. In the first two quarters of 2005, 3619 patients were started on ART. The data illustrates the temporal trends across these cohorts. The percentage of patients dying in the first 6 months of treatment was 12.7%, 12.6%, 11.4%, 5.4%, and 5.2% in 2001, 2002, 2003, 2004 and 2005 respectively.

Poisson regression analysis of adult data showed an incidence rate ratio (IRR) of 1.02 for death at 6 months on ART for every 1% increase in the proportion of patients with a baseline CD4 count < 50 cells/mm^3.

B. Children

This study reported on 1271 children started on treatment before the end of July 2005; this is 81.6% of the total number of children enrolled onto ART during that period of whom 38.9% had a CD4 count < 50 cells/mm^3.

92.7%, 89.6%, 87.5%, 93.8% and 92.3% of children were still in care at 3, 6, 12, 24, and 36 months respectively. The cumulative death rates for children on treatment at these monthly intervals were 5.2%, 8.2%, 9.5%, 4.7% and 7.7% respectively. The percentage of patients on second line treatment was low (0.1% at 6 months and 0.4% at 12 months). The percentage of children with a CD4 count > 20% peaked at 86.8% amongst children on ART for 12 months. Viral load suppression rates were consistently between 70% and 80%, and peaked at 78.3% amongst those children on ART for 30 months.

The number of patients started on ART from 2001 to 2004 was 6, 32, 36, and 737 in each year respectively; there was a significant decrease in the proportion of children with a CD4 < 50 cells/mm^3 from 2003 to 2004. The percentage of patients who were treatment experienced increased from 5.9% in 2002 to 15% in 2004. The percentage of children dying in the first 6 months of treatment was 8.5% and 7.6 % in the 2004 and 2005 cohorts respectively.

Conclusions

Patient retention and survival rates are good and in keeping with similar studies in both resource-limited and wealthy countries. There was a trend toward improving baseline characteristics (e.g. CD4 count) from 2001 to 2005, reflecting the earlier recruitment of patients; which is in turn reflected in significantly improved outcomes in the adult data.

Background

1.1 Introduction

The state of the HIV epidemic in South Africa

HIV/AIDS is the largest single contributor to the burden of disease in South Africa and is fuelling the already critical tuberculosis (TB) epidemic [1]. The WHO has estimated that the adult prevalence of HIV/AIDS in South Africa increased from less than 1% in 1990 to almost 25% in 2000 [2]. A Joint United Nations Programme on HIV/AIDS* (UNAIDS) report claimed that in July 2005 85% of patients (900 000 adults and children), who should have been on ART in South Africa, were still not on treatment [3]. UNAIDS HIV prevalence estimates are calculated from antenatal prevalence using the 'spectrum software programme' [4].

In 2000 HIV / AIDS was estimated to be responsible for 30% of deaths in South Africa, 38% of 'years of life lost' (YLL) and a loss of 'Disability adjusted life years' (DALY's) in excess of 5 million [1].

However, as outlined below, uncertainty as to the true prevalence of HIV in South Africa exists.

* UNAIDS, the Joint United Nations Programme on HIV/AIDS, is an innovative joint venture of the United Nations family, bringing together the efforts and resources of ten UN system organizations in the AIDS response to help the world prevent new HIV infections, care for people living with HIV, and mitigate the impact of the epidemic [5].

The population of the Western Cape Province is 3.4 million. Voluntary counseling and testing (VCT) for HIV is widely available in the public health system and in the 2004/5 financial year 210 000 people were tested (82% of the provincial target). Of those tested 35 000 were positive (%positive rate = 17%). Generalization of this prevalence rate to the general population is inappropriate [6].

The National Department of Health (NDOH) Antenatal Survey is conducted in all nine provinces annually. The national HIV prevalence amongst women attending antenatal clinics in 2003 was 27. 9%. The Western Cape prevalence was lower at 13.1%. The 2003 antenatal survey did not detail the number of patients who declined HIV testing. Extrapolation from antenatal data to the general population is also not accurate [7].

The Stats SA report (2002) described the recent emergence of a mortality peak amongst 25 to 35 year olds in South Africa; it ascribed this new peak to the following causes of death as noted on the death certificate:

- Unspecified cause
- HIV/AIDS
- Tuberculosis & pneumonia

The report did not make predictions about the constituents of unspecified cause [8].

A Medical Research Council (MRC) study (2001) made the following comments: 'The validity of mortality data in South Africa is poor, especially in

respect to HIV/AIDS. This is due to failure of the Department of Home Affairs to register reported deaths and the incorrect filling in of cause of death on the death certificate'. There was however an improvement in the registration of deaths by the Department of Home Affairs between 1990 and 2000, with the coverage improving from 54% to 89%. The report further hypothesized that the only feasible explanation for the change in the mortality pattern is HIV / AIDS and predicted that the increase in the number of HIV/AIDS related deaths over the next decade would lead to a cumulative incidence of HIV / AIDS related deaths of 5 to 7 million by 2010 [9].

The debate around the true prevalence of HIV/AIDS in South Africa makes prediction of the number of patients who should be on ART difficult; however as outlined in the UNAIDS report cited above the demand for ART in South Africa far outstrips its current availability [2, 3].

The WHO recognises the positive impact that ART has had globally on reducing the impact of HIV/AIDS; it estimated that by July 2005 250 000 to 350 000 deaths had been averted as a result of the availability of ART [2, 3]. The NDOH's guideline for the treatment of HIV/AIDS, published in 2004, recognised the important role played by ART [10].

The first patients started on ART in the Western Cape Province public health service began treatment as early as January 2001. These patients were funded jointly by government and non-government sources, such as the DTF and MSF, on account of the then limited availability of government funding for

ART. Since 2005 the funding of patients has been largely taken over by the state, although donors have continued to make significant funding contributions.

The government funded rollout of ART in South Africa began in April 2004. Patients in the Western Cape are treated in accordance with provincial guidelines at almost all facilities. Some sites use modified protocols, allowing for amongst other things more frequent testing of viral loads. The majority of ART facilities are primary care sites, although some of these operate within the confines of secondary and tertiary hospitals.

At the start of the rollout 787 children and 1552 adults were already on ART; by the end of September 2005 these numbers had increased to 1663 and 12 063 respectively. The increase in patients on ART during this time was facilitated by the increase in the number of operative ART sites from 20 in March 2004 to 37 in September 2005.

Treatment protocols

The Western Cape provincial protocol is the same as the National ART protocol. Adults are eligible for ART if they have a CD4 count < 200 cells/mm^3 or are WHO stage 4 AIDS. Treatment naive adult patients in the public sector are started on Stavudine (D4T), Lamivudine (3TC) and Efavirenz (EFV), unless there are contraindications in which case alternate regimens are available (4). Pregnant women or women planning pregnancy are given Nevirapine (NVP) in place of EFV, as EFV is thought to be teratogenic in early

pregnancy. The ART protocol makes allowance for one formal change to a second line regimen. In practice the scope for change is greater, as informed single drug changes may be made by specialist clinical staff [11].

Patients are screened for TB before starting ART. With patients on concomitant TB treatment ART should ideally be postponed till the end of the initial two month intensive treatment phase; however if the clinical indications for starting ART are urgent then treatment should be commenced, avoiding regimens with NVP because of an increased risk of hepatotoxicity when used with Rifampicin [11].

Table1: Guidelines for antiretroviral treatment of adults

	Not pregnant	Pregnant or planning pregnancy
First Line	Stavudine (D4T)	Stavudine (D4T)
	Lamivudine (3TC)	Lamivudine (3TC)
	Efavirenz (EFV)	Nevirapine (EFV)
Second line	Didanosine (DDI)	Didanosine (DDI)
	Zidovudine (AZT)	Zidovudine (AZT)
	Kaletra (Kal)	Kaletra (Kal)

When starting children on ART more emphasis is placed on clinical and social criteria than in adults as outlined below.

Clinical criteria (children must meet at least one criterion)

- Recurrent (>2 admissions per year) hospitalisations or prolonged hospitalisation (>4 weeks) for an HIV related illness
- WHO stage 3 or 4
- CD4 count < 20% (< 18 mths) or < 15% (if > 18 mths)

Social criteria (these must be met in addition to the clinical requirements)

- At least one identifiable caregiver who is able to supervise the administration of all medication
- Disclosure to at least one adult in the house where the child is living

Table 2 below shows available first line regimens for children.

Table 2: Guidelines for antiretroviral treatment of children

Age	< 6 months	> 6 months
First Line	Stavudine (D4T)	Stavudine (D4T)
	Lamivudine (3TC)	Lamivudine (3TC)
	Ritonavir	Lopinavir/Ritonavir
Second line	(Didanosine)DDI	(Didanosine)DDI
	AZT (Abacavir (ABC) if no fridge)	AZT (Abacavir (ABC) if no fridge)
	NVP	EFV

NVP should be used in place of Lopinavir/Ritonavir if the child has not been exposed to NVP during Prevention of Mother to Child Transmission (PMTCT). In children on TB treatment Lopinavir and Nevirapine should be avoided [11].

Importantly, the ART treatment protocol outlines a 4 week work-up period for all patients starting ART treatment. Patients may be fast tracked for clinical reasons, such as advanced disease or pregnancy. The protocol prescribes the checking of CD4 count and viral load at baseline and then at 6 monthly intervals [11].

Description of the monitoring system

The paper based monitoring system was introduced in April 2004 in conjunction with the ART rollout. The paper tools of the monitoring system comprise:

- the ART register (Appendix A)
- the quarterly report form (Appendix B)
- structured clinical records (Appendix C)
- the patient held card (Appendix D)

(The paper tools are also visible on the University of Cape Town website: www.epi.uct.ac.za/artrollout)

The tools were developed and implemented jointly by staff from the Department of Public Health at the University of Cape Town and the HIV directorate of the PGWC. Training was provided through site visits, workshops and a training manual developed by the above mentioned stakeholders.
The rationale for using CD4 and viral load counts for monitoring disease progression is outlined in Box 2 and the WHO clinical staging criteria in Boxes 3 and 4.

Box 1: Pathogenesis and monitoring of HIV / AIDS [12]

The HIV virus is spread through blood and blood products, sexual contact and by transmission from mother to child. The virus attaches to the CD4 cell in the blood. The CD4 cell is a lymphocyte which is in turn a component of the white blood cells. The HIV virus uses the CD4 cell as a host in which to replicate. As the viral count increases the CD4 cells are damaged and killed which in turn leads to decreased immunity for the infected individual.

The WHO staging criteria are used for clinical monitoring if HIV / AIDS. In countries that can afford it immunological monitoring is performed using the CD4 count and viral load count which reflect the activity outlined above. The percentage of lymphocytes that are CD4 cells is used in children as this more accurately reflects disease progression.

Antiretroviral inhibit viral load replication sparing the CD4 cells. CD4 count and viral load are acknowledged as the best markers of disease progression.

Box 2: WHO clinical staging criteria for adults [11].

Stage One
1. Asymptomatic (ASY)
2. Persistent generalised lymphadenopathy (PGL)
3. Acute retroviral infection (seroconversion illness) (ARI)
Stage Two
4. Unintentional weight loss < 10% of body weight (WL4)
5. Minor mucocutaneous manifestations, e.g. seborrhoea, prurigo, fungal-nail, oral ulcers, angular cheilitis (MMC)
6. Herpes zoster within the last five years (HZV)
7. Recurrent upper respiratory tract infection, e.g. bacterial sinusitis (URTI)
Stage Three
8. Unintentional weight loss > 10% of body weight (WL8)
9. Chronic diarrhoea > one month (DIA)
10. Prolonged fever > one month (PYR)
11. Oral candidiasis (ORC)
12. Oral hairy leukoplakia (HLP)
13. Pulmonary TB within the last year (PTB)
14. Severe bacterial infections, e.g. pneumonia (BAC)
15. Vulvovaginal candidiasis > one month / poor response to therapy (VVC)
Stage Four
16. HIV wasting (8+9 or 10) (CAC)
17. Pneumocystis carinii pneumonia (proven: PCP, presumptive: PPCP)
18. CNS toxoplasmosis (TOXO)
19. Cryptosporidiosis + diarrhoea > one month (CRS)
20. Isosporiasis + diarrhoea (ISO)
21. Cryptococcosis - non pulmonary (CRC)
22. Cytomegalovirus infection other than liver, spleen or lymph node (CMV)
23. Herpes simplex infection; visceral or > one month mucocutaneous (HSV)
24. Progressive multifocal leucoencephalopathy (PML)
25. Disseminated mycosis (MYC)
26. Oesophageal / tracheal / pulmonary candidiasis (OEC)
27. Atypical mycobacteriosis disseminated (MOTT)
28. Non-typhoidal Salmonella septicaemia (SAL)
29. Extra-pulmonary tuberculosis (ETB)
30. Lymphoma (LYM)
31. Kaposi's sarcoma (KS)
32. HIV encephalopathy (ADC)
33. Invasive cervical carcinoma
34. Recurrent pneumonia

Box 3: WHO clinical staging criteria for children [11].

Stage One

1. Asymptomatic
2. Generalized lymphadenopathy
3. Hepatomegaly
4. Splenomegaly
5. Hepatosplenomegaly

Stage Two

6. Unexplained chronic diarrhoea (≥ 2 weeks)
7. Failure to thrive
   - 60-80% expected body weight
   - Not responding to nutritional rehabilitation or anti-TB therapy (if clinically indicated). Other correctable causes excluded
8. Recurrent or severe bacterial infection (≥ 2 episodes pneumonia or 1 episode meningitis)
9. Oral candidiasis beyond neonatal period
   - Severe persistent or recurrent, not responding to topical therapy
10. Persistent fever (≥2 weeks)
11. Haematological
    - Thrombocytopenia (platelet count < 40 000 X 10^9/L) not responding to prednisone 2 mg/kg/day after 2 weeks
    - Neutropenia (neutrophil count < 500 X 10^9/L) not responding to switch from co-trimoxazole to dapsone
12. Severe lymphoid interstitial pneumonitis with clubbing
13. ≥ 2 episodes Zoster or severe herpetic disease
14. Otorrhoea > 6 weeks
15. Single episode of proven or probable tuberculosis

Stage Three

16. AIDS opportunistic infection
17. Severe failure to thrive
    - < 60 % expected body weight
    - Not responding to nutritional rehabilitation or TB therapy if clinically indicated
18. Progressive encephalopathy
19. Recurrent septicaemia (≥ 2 episodes)
20. Bronchiectasis (clubbing and persistent nocturnal cough)
21. Cardiomyopathy
22. Progressive nephropathy
23. Candidiasis (oesophageal or pulmonary).
24. Disseminated fungal infection (Coccidioidomycosis, Cryptococcosis, Histoplasmosis)
25. Disseminated mycobacterial infection (M. tuberculosis, BCG, avium-intracellulare, Kansasii)
26. CMV disease with onset at age > 1 month (at site other than lymph nodes, spleen, liver).
27. HSV causing mucocutaneous ulcer persisting > 1 month, or bronchitis, pneumonitis, oesophagitis in a child older > 1 month.
28. Pneumocystis carinii pneumonia (PCP)
29. Progressive multifocal leukoencephalopathy.
30. Recurrent pulmonary tuberculosis

Every patient who starts ART at a public health facility should be entered into the ART register by facility based data staff. Patients are assigned to cohorts based on the date on which they started ART. These cohorts are of 3 months duration. The patient data in the ART register should be updated at 6 monthly intervals. The register is then used to complete the quarterly reports.

Quarterly reports detail the following:

1. **Cumulative death rate**
2. **Cumulative rate of loss to follow up**
3. **Cumulative percentage of patients on a 2nd line regimen**
4. **Cumulative number of patients transferred out to another site**
5. **Percentage of patients in care with a CD4 count reported in the register**
6. **Percentage of CD4 counts reported that are < 200 cells/mm^3**
7. **Percentage of patients in care with a viral load reported in the register**
8. **Percentage of viral loads reported that are < 400 copies/ml**

Data in the quarterly reports is aggregated at facility level. This aggregation was introduced to simplify the reporting process as each facility submits a single page report on a quarterly basis. Getting individual level date from each facility would not have been feasible with the paper based system. These reports are faxed or emailed to the Provincial Government of the Western Cape Monitoring and Evaluation (M&E) Unit where data is entered into a Microsoft Excel™ database. Analysed reports are presented to management quarterly.

At sites using electronic databases the required data for the quarterly reports has been extracted and assimilated with data from the paper based system in the database. Data on patients who started ART prior to April 2004 has also been assimilated in this manner.

Outcome data (a summary of this data is provided in table 3)

1. Outcome data from developed countries

Ledergerber et al (1999) reported on their study of a cohort of Swiss patients. The study had followed 2674 patients for a median of 36 months. They found a viral load suppression rate of 90.7% in treatment naive adults at 12 months on ART and 80% at 24 months. Suppression rates amongst treatment experienced patients ranged from 70.3 to 78.7%. At two years of ART 20.1% of treatment naïve patients had viral rebound (2 consecutive viral load measurements > 400 copies/ml). The percentage of patients in the treatment experienced group experiencing viral rebound at 24 months was almost double, ranging from 37 to 40% [13].

Chan et al (2002) followed up 1219 patients in British Columbia and 5110 patients in the United States. This study showed Kaplan Meier survival rates of 93.4% and 80.9% at 24 months in the respective cohorts. A baseline CD4 count < 200 cells/mm^3 was shown to have a significant negative impact on survival when compared to a baseline CD4 count > 500 cells/mm^3 [14].

Schrooten et al (2005) followed 225 patients started on ART in Belgium in 1997. The mean CD4 count at baseline was 280 cells/mm^3. After 5 years of

treatment 79% had viral loads < 400 cells/mm^3 and the mean increase in CD4 count was 333 cells/mm^3. Patients who had a treatment interruption of more than 7 days showed a significantly smaller increase in CD4 count [15].

Sterne at al (2005) published a more recent study of the original Swiss cohort following up 3437 patients. It compared patients on ART vs. those on no treatment and those on dual therapy. The overall hazard rate for progression to AIDS or death was 0. 14 (95% CI's 0.07 to 0.29) when comparing triple therapy to no treatment when followed up for a median of 27 months. The hazard ratio for patients on treatment for > 24 months was 0.04 (95% CI's 0.01 to 0.09) [16].

2. Outcome data from developing countries

Laurent et al (2004) reported on a multi-centre study in Cameroon which looked at the effectiveness of a fixed dose ART combination. The primary outcome was a viral load < 400 copies/ml. 60 patients were followed up over 24 weeks. At 12 weeks of ART 75 % of patient viral loads were suppressed and at week 24 80% of patient viral loads were suppressed. 1 patients' ART was stopped because of side effects and 2 were changed to second line treatment. This study reported a mean adherence of 99% and the authors felt that the fixed dose combination was causal in this high rate [17].

Coetzee et al (2004) published a study which followed 287 adults in Cape Town for a median of 13.9 months. The median CD4 count at baseline was 43 cells/mm^3. The percentage of patients with a viral load < 400 copies/ml was

88.1, 89.2, 84.2, 75.0 and 69.7 at 3, 6, 12, 18 and 24 months respectively. The cumulative probability of remaining on treatment at 2 years was 86.3%. The cumulative probability of changing one antiretroviral was 15.1% at 2 years. The patients studied in the Coetzee paper have contributed to the data in this report [18].

A study by LG Bekker et al (2006) of adults on ART in Cape Town showed very positive results. The data showed an improvement in the baseline characteristics of patients from 2002 to 2004, with the mean CD4 count amongst patients starting treatment at Gugulethu Day Hospital increasing from 84 to 89 and to 110 cells/mm^3 in 2002, 2003 and 2004 respectively; this increase was however not statistically significant. There was a reduction in the percentage of patients who were WHO stage 3 or 4 from 90% in 2002 to 76% in 2004 reflecting the earlier enrolment of patients onto treatment. The overall percentage of patients lost to follow up over this time period was 2.9%; Kaplan Meier estimates of the proportion of patients remaining in the programme was 82%, 86% and 91% in the 2002, 2003 and 2004 cohorts respectively at the time of censoring (September 2005). The percentages with viral loads <400 cells/mm^3 were 100%, 92% and 98% at the time of censoring for these respective cohorts. It should again be noted that patients reported in the Bekker study also contributed to the data reported in the monitoring system (5). Orrell et al reported a mean adherence rate of 93.5% amongst 289 patients from the same cohort. In addition the study showed that three times daily dosing, not speaking English and young age were found to be

independent risk factors for non adherence. Low socioeconomic status, sex and WHO stage were found not to be significant predictors of adherence [19].

Wools-Kaloustian (2006) reported on clinical and immunological outcomes of 2055 adult ART patients in Kenya for a median follow up period of 40 weeks. The death rate in this cohort was 5. 4% and the loss to follow up rate 24.5%. Only 74.5% of patients were found to be adherent. The study documented mean increases in CD4 count of 160 cells/mm^3, 225 cells/mm^3 and 297 cells/mm^3 at 12, 24 and 36 months of ART respectively [20].

Weidle et al (2002) followed up 476 patients on ART in Uganda. Their study confirmed that a CD4 count < 50cells/mm^3 at baseline was significantly associated with an increased death rate (Hazard ratio 2.95, $P < 0.001$). The study reported high rates of loss to follow up, with only 49% of patients remaining in care at 12 months of treatment [21].

The ART-LINC study (2006) compared outcomes between 12 adult cohorts from developed and developing countries and confirmed that the provision of ART in developing countries is feasible. It found that patients from lower income settings had a significantly lower baseline CD4 count. The hazard ratio of death adjusted for baseline factors, including baseline CD4 count, was significantly higher amongst cohorts from developing countries until 6 months of ART; after this duration of treatment there was no significant difference in survival (Proportional hazard=1.5; 95% CI 0.7 to 3). However patients lost to follow up were excluded from analysis [22].

Paediatric data

A study by Doerholt et al (2006) followed 125 children in the UK on either 3 or 4 drug regimens and found that only 59% had a viral load < 400 copies/ml at 12 months. They also found that the median CD4 increase during this period ranged from 24% to 35% [23].

Matida et al (2004) analysed routine data on 914 HIV positive children in Brazil. They found that the survival of HIV positive children was significantly increased with the introduction of ART in 1997. Before this time 50% of HIV positive children were dead at 20 months of illness; after this date 75% were still alive after 48 months of illness. Although this paper convincingly showed an increased survival, it did not unpack the individual reasons for this difference [24].

Fassinou et al (2004) followed 78 children on ART in the Ivory Coast, for a mean duration of 21 months. The probability of survival with ART was 92.3%, 91%, 88.1% and 88.1% at 6, 12, 18 and 24 months respectively. After 2 years of ART only 60% of patients had a viral load < 300 copies/ml [25].

Eley et al (2004) reported on initial experiences in treating children with HAART in Cape Town. Results showed a significant drop in viral load for 12 children after 6 months on ART, as well as a significant increase in CD4 count. Adherence was mostly greater than 85%. After 12 months no severe drug reactions were reported. Results from this study were promising, but

limited by sample size. Once again the monitoring system includes data from these children [26].

Puthanakit et al (2005) followed 107 children on ART in Thailand from August 2002 to July 2003. They found that after 18 months of ART 76% of patients had a viral load < 50 copies/ml. 86% of patients were adherent (taking at least 95% of tablets). The article concludes that the outcomes in Thailand are comparable with those from first world countries [27].

Table 3: Summary of published follow up data for ART patients

Table 3 : Summary of published follow up data for ART patients

Author	Year	Country	Study type	Sample size	Coments
Adult patients					
Lederberger	1999	Swiss cohort	Cohort	2674	VLS in naïve patients 80% at 2 yrs
Sterne	2005	Swiss cohort	Cohort	3437	Hazard ratio for death 0.14, ART vs no ARV.
					Median FU 27 mths
					VLS in ART exp patients 60 to 63% at 2 yrs
Chan	2002	Canada	Cohort	1219	KP survival est at 2 yrs = 93.4%
		USA	Cohort	5110	KP survival est at 2 yrs = 80.9%
Schrooten	2005	Belguim	Cohort	225	VLS 79% at 5 years
Weidle	2002	Uganda	Cohort	476	RIC 49% at 12mths
Laurent	2004	Cameroon	Cohort	60	VLS 75%, 12wks
					VLS 80% at 24wks
Coetzee	2004	South Africa	Cohort	287	VLS 89% at 1yr
					VLS 75% at 2 year
					RIC 86.3% at 2 yr
Bekker	2006	South Africa	Cohort	1139	KP est RIC 91% at 1 yr
					KP est RIC 86% at 2 yr
					KP est RIC 82% at 3 yr
Wools-Kaloustian	2005	Kenya	Cohort	.	RIP 5.4%, LTF 24.5%, Median FU 40wks
Children					
Matida	2004	Brazil	Routine data	914	Survival increased with ARV
Fassinou	2004	Ivory Coast	Cohort	78	91% survival at 12 mths
					88.1% at 24 mths
					VLS at 24mths 60%
Eley	2004	South Africa	Routine data	12	Good adherence (>85%)
Punthanakit	2005	Thailand	Cohort	107	VLS 76% at 12mths
Doerholt	2006	UK	Cohort	125	VLS 59% at 12 months
ARL-LINC	2006	Global	Multiple cohorts	12 cohorts	Prop haz for death Developed vs developing < 6mths ART= 1.5

* Abbreviations: VLS-viral load suppresion rate, RIC- remaining in care; RIP-death; LTF-lost to follow up; FU-follow up; KP-Kaplan Meier

Conclusions from the literature review

Table 3 summarises the outcomes from cited follow up studies. The literature from the developed world shows high rates of viral load suppression and patient retention (Swiss 90.7%, British Columbia 93.4% and USA 80.9% at 2 years on ART). Results from the developing world are more varied. In the South African data rates of patient retention and viral load suppression were similar to those in the studies cited above. However the results from the Ugandan and Kenyan studies were less impressive with high rates of loss to follow up (24.5% in Kenya and 51% in Uganda).

There is a paucity of good follow up studies of children on ART. The studies reported here showed a wide range of survival and viral load suppression,

with some of the highest rates of suppression reported from countries in the developing world. As is shown in the literature summary standardization of outcomes would facilitate better comparison across studies.

1.2 Motivation for this study

There has been an extensive scaling up of the ART programme in the Western Cape since April 2004. This study seeks to investigate the clinical outcomes of patients on ART in the public health sector in this province. The importance of this is illustrated by the article cited above where the incidence of key outcomes such as death and loss to follow up has reached undesirably high levels in some programmes.

1.3 Aims and objectives of the study

Aim of this study

To describe and analyse the data produced by the routine monitoring system for ART in the Western Cape Province, South Africa.

Objectives of this study

1. To describe baseline characteristics of patients on ART
2. To describe the cumulative incidence of the following events in patients on ART:
    - Death
    - Loss to follow up
    - Change to a second line ART regimen
    - Transfer out to another ART site

- The proportion of viral loads reported in the register
- The proportion of viral loads that are suppressed
- The proportion of CD4 counts reported in the register
- The proportion of CD4 counts > 200 cells/mm^3 at specified durations of treatment

3. To describe and analyse temporal trends in the data.
4. To describe and analyse the impact of baseline characteristics on mortality rates at 6 months of ART.

Methods

Definition of terms

- **Adherent**: taking > 85% of ART tablets.
- **Child:** is a patient less than or equal to 14 years of age. This cut off was chosen as it is the age at which the patients routinely enter the adult services.
- **Lost to follow up** (LTF): means that the patient has missed an appointment and not been contactable for 3 months subsequent to that date. The 3 month delay is to allow for patients who have been unable to attend the clinic for logistic or other reasons to re-attend.
- **Region**: The Western Cape Province is divided into four regions viz. the Metro, the South Cape / Karoo, the West Coast / Winelands and the Boland / Overberg.
- **Transfer out** (TFO): is when a patient is electively transferred to another site with no break in treatment and the necessary handover, which includes a referral letter.
- **Transfer in** (TFI): is when a patient is transferred in from another ART site
- **Treatment experienced:** means that the patient has had prior exposure to ART for more than one month. This does not include exposure of mothers and infants during PMTCT.
- **Treatment failure**: Viral load > 1000 copies/ml (PGWC monitoring report)

Study Design

The data for this report is provided by a routine monitoring system and analysed by simplified cohort analysis. Simplified cohort analysis follows cohorts of patients and measures the incidence of defined outcomes at specified intervals, in this case every 6 months in a series of cross sectional analyses. All patients who have reached 6 months of treatment are reported at 6 months irrespective of the date on which they reached this duration on ART. For example some patients reached 6 months of treatment in 2004 and some in 2005. When reporting 6 month outcomes these patients are considered together [28]. Data captured in the monitoring system is aggregated at a facility level, the rationale for this related primarily to keeping data collection as simple as possible to reduce the burden on data staff.

Sampling

All patients started on antiretroviral treatment in the public sector (the entire ART population) were included in the study sample. Patients who started on treatment prior to the rollout in April 2004 have been included in this study. The data for these patients was retrieved retrospectively from electronic databases. The study sample therefore includes data on patients started on treatment between January 2001 and June 2005.

Patients who have been transferred in from one site to another have been excluded from analysis at their new facility as the data relating to these patients is often incomplete. Similarly patients who are treatment experienced

are not included in the analysis as the published literature suggests they have differing clinical characteristics [13, 19, 22].

The paper based system

The paper based system is introduced in the introduction. The aggregation of data at facility level has been a vital consideration in the analysis of the data and should be kept in mind at all times as it has necessitated working with proportions. For the proportions the numerator was the number of patients experiencing an event and the denominator the total number of patients on treatment at that facility. This proportion has in some cases been converted to a percentage for easier interpretation.

Outcomes are calculated cumulatively, for example a patient dying between 0 and 6 months is recorded as dying by 6 months. Submission of cohort reports is requested 3 months after the closure of the time period being studied to allow for the correct classification of outcomes, e.g. defining of lost to follow up, and time for the laboratory results to be returned from the laboratory and entered into the register.

The 'transfer in' patients are entered in the ART register with their original cohort, i.e. if they started in January 2005 they are entered with other patients started in January 2005. However, sometimes patients are transferred in to sites that only opened after the date on which they were commenced onto ART. These patients are entered onto a separate page in the register, specifically reserved for transfer in patients meeting these criteria.

Analysis of data

Adults and children have been analysed separately in recognition of differences in the clinical course of these two groups on ART. Data was analysed to determine longitudinal trends, temporal trends and the impact of baseline characteristics on death rates at 6 months of ART.

Stata 8^{TM} was used to conduct analysis. Longitudinal regression using the *Stata xtpoisson* commands was used to assess the impact of the baseline characteristics on the incidence rate of death at 6 months. This duration of treatment was chosen as it provides a large sample size and captures a significant proportion of patients started after April 2004. In the regression model the total number of patients in the cohort was used as the exposed group (to ART) as there were no unexposed patients in the data. The random effects model was chosen over the population averaged model as the facility at which the patients were treated was likely to have an impact on outcomes.

Summation of totals was used for validation. For example, at a specified duration of treatment the number of patients remaining in care should equal the number enrolled minus (deaths + number of patients transferred out + the number of patients lost to follow up) prior to that duration.

Ethics

This report uses routine data collected by the M&E Unit of the HIV Directorate of the PGWC. Ethical permission for the use of the data was granted by the University of Cape Town ethics committee.

Anonymity is strictly observed as the data is completely anonymous and in aggregate form. This prevents the results of the study harming individual participants.

This report analysis contained in this report should be used to identify problems in the programme.

The data has been analysed and shared with the relevant stakeholders to make sure that the programme and ultimately the patients themselves benefit from the results.

Comprehensive analysis and subsequent interventions based on this data will further justify the resources used in the running of the monitoring system.

Results

A. Adults

This report includes data on 97.5% of adult patients starting ART between January 2001 and the end of July 2005.

1. Baseline cohort data (Patients enrolled from January 2001 to end July 2005)

A total of 8698 adults were captured by the monitoring system by the end of July 2005 in the WC Province. Of these 32.4% were men and 67.6% were women. Across the cohorts 22.5% of those who started treatment had a CD4 count < 50 cells/mm^3 and 3.6% of patients enrolled were considered treatment experienced and excluded from follow up analysis.

Figure 1: Percentage of adults remaining in care by duration of treatment

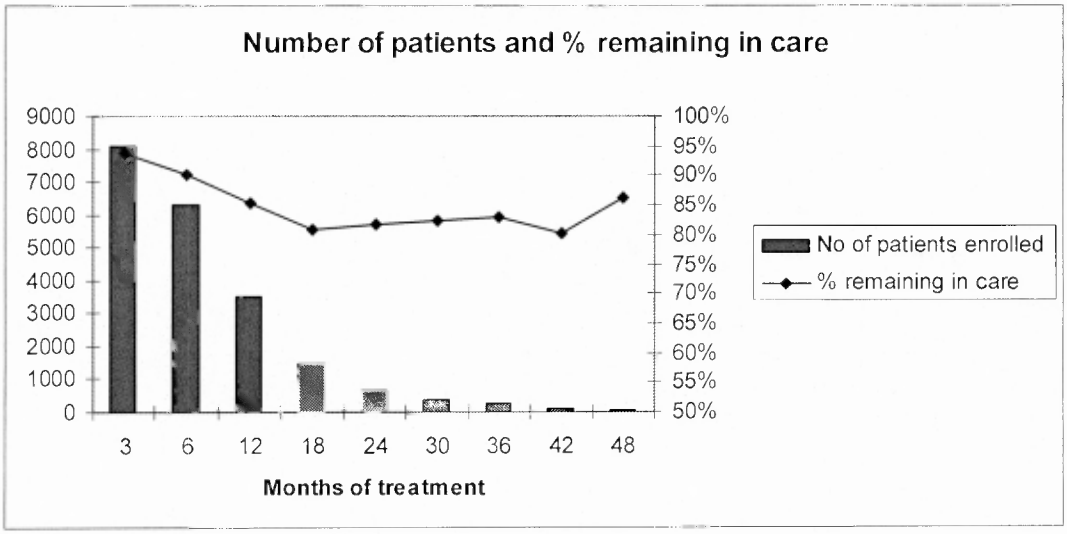


Figure 1 describes the number of patients in care at increasing durations of ART and the percentage of patients remaining in care. It also shows that the number of patients eligible to reach a designated duration of treatment decreased as the duration on ART increased.

2. Longitudinal trends

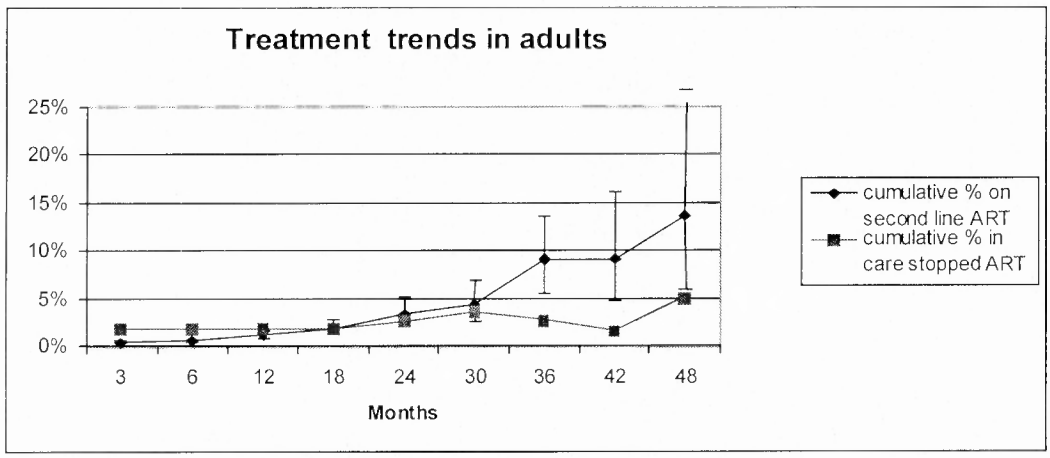
Figure 1 also shows that patient retention was high (> 80%) even for patients on ART > 24 months. Patients no longer in care may have died, been lost to follow up or been transferred out.

2.1 Treatment trends

Table 4: Percentage of patients on 2nd line treatment and percentage in care, but not on ART, by treatment duration

Duration on treatment	Total patients on treatment	Patients on second line treatment		In care ART stopped
Months		%	95% CI's	%
3	8100	0.4%	0.3 to 0.5%	1.8%
6	6308	0.5%	0.3 to 0.7%	1.9%
12	3507	1.2%	0.9 1.7%	1.9%
18	1444	1.8%	1.2 to 2.6%	1.9%
24	646	3.4%	2.1 to 5.2%	2.6%
30	392	4.3%	2.5 to 6.9 %	3.6%
36	246	8.9%	5.6 to 13.5%	2.8%
42	130	9.2%	4.8 to 16.1%	1.5%
48	59	13.6%	5.9 to 26.7 %	5.1%

Figure 2: Percentage of patients on second line and percentage in care, but not on ART by treatment duration



By 12 months of ART only 1.23% of patients were on second line treatment; at 24 and 36 months the percentages were 3.4% and 8.9% respectively. The difference was statistically significant between the 12 to 24 and 24 and 36 month cohorts.

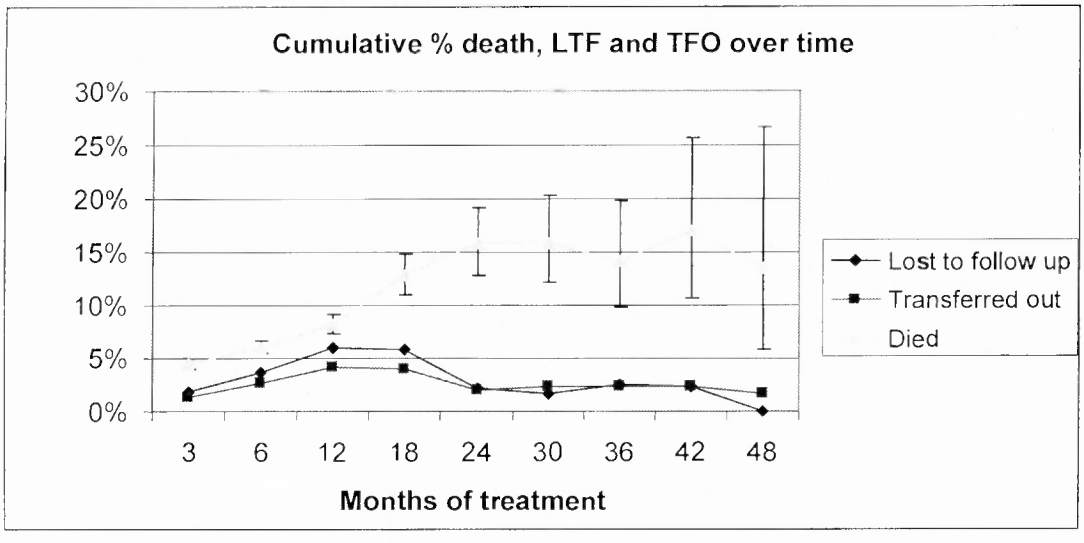
The percentage of patients remaining in care at the ART clinic, but no longer on ART, is also shown above. Once again the percentages were low (<5%). Medication is most likely to have been stopped due to adverse events; however reasons for stopping treatment are not recorded by the monitoring system.

2.2 Death, loss to follow up and transfer out

Table 5: Death, loss to follow up and transfer out of adults on ART

Duration on treatment	Total Patients on treatment	Patients dead		Patients lost to follow up	Patients transferred out	Patients remaining in care
Months	Total	%	95% CI	%	%	%
3	8100	4.5%	4.0 to 5%	1.9%	1.3%	93.6%
6	6308	6.1%	5.5 to 6.7%	3.7%	2.6%	90.1%
12	3507	8.2%	7.3 to 9.3%	6.0%	4.2%	85.4%
18	1444	12.8%	11.0 to 14.8%	5.8%	4.0%	80.9%
24	646	15.8%	12.9 to 19.2%	2.2%	2.0%	81.7%
30	392	15.8%	12.1 to 20.3%	1.6%	2.3%	82.2%
36	246	14.2%	9.9 to 19.8%	2.5%	2.4%	82.9%
42	130	16.9%	10.6 to 25.6%	2.4%	2.3%	80.3%
48	59	13.6%	5.9 to 26.7%	0.0%	1.7%	86.2%

Figure 3: Death, loss to follow up and transfer out of adults on ART



The data shows that the cumulative death rate increased significantly between the 3 month and the 18 month cohorts (4.5% to 12.8%). After this the rate increased in the 24 month cohorts and then stabilized around 15 %. The

differences in death rates amongst patients reaching varying durations of treatment, longer than 18 months, were not statistically significant.

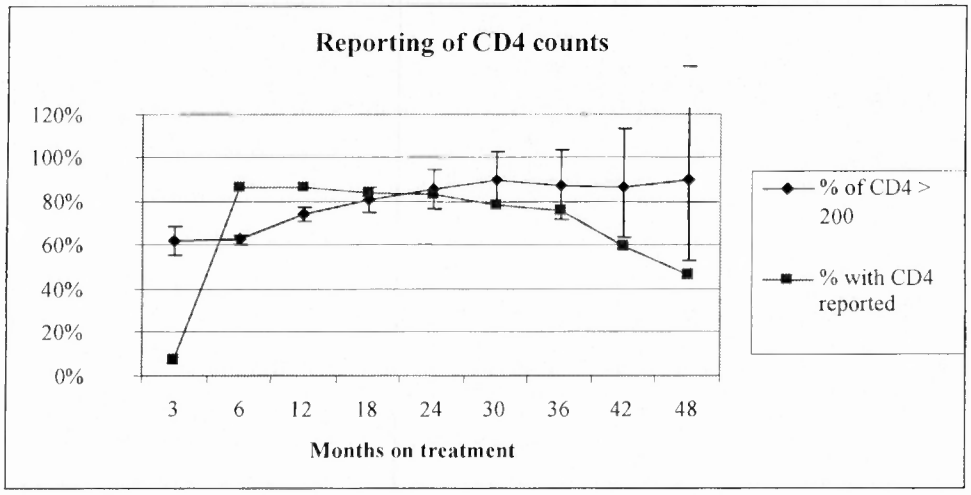
The percentage of patients lost to follow up was highest amongst those cohorts reaching 12 months of ART (6%). The rate of loss to follow up was lower amongst cohorts on ART for longer durations, reflecting the better retention of patients from earlier cohorts. The change in the proportion of patients being transferred out followed a similar pattern.

2.3 Immunological outcomes

Table 6: CD4 results for adults on ART

Duration in months	CD4's reported in ART register	%CD4 completed (CD4 reported / patients on treatment)	%CD4>200 cells/mm^3 (CD4>200/CD4 reported in ART register)
	No.	%	% & 95%CI
3	536	7.3%	61.8% (55.3% to 68.8%)
6	4642	86.3%	62.5% (60.2% to 64.8%)
12	2398	86.5%	74.2% (70.8% to 77.7%)
18	921	84.3%	80.7% (74.9% to 86.7%)
24	414	83.5%	85.5% (76.8% to 94.9%)
30	232	78.4%	90.1% (78.3% to 103.2%)
36	138	75.8%	87.0% (72.2% to 103.9%)
42	58	59.8%	86.2% (63.9% to 113.7%)
48	20	46.5%	90.0% (53.4% to 142.2%)

Figure 4: CD4 results for adults on ART



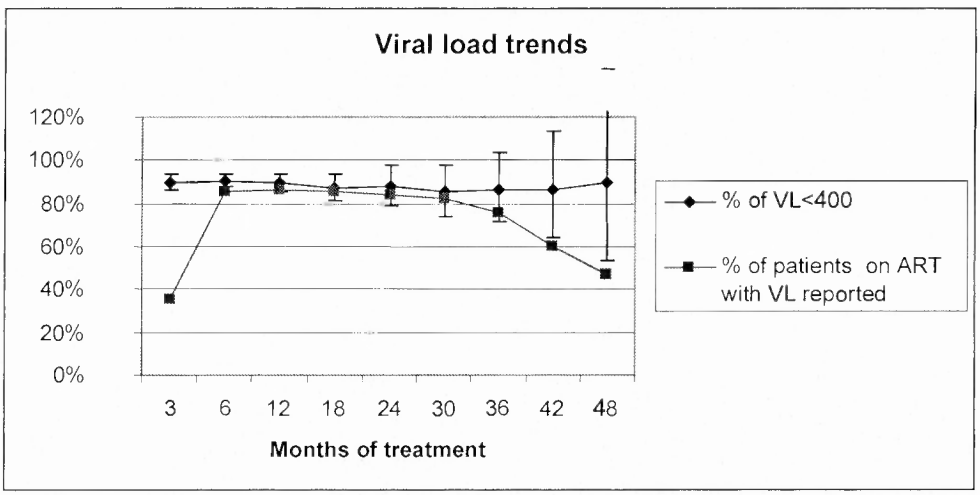
The percentage of patients on treatment with CD4 counts reported remained above 80% amongst those patients on treatment for less than 30 months. The reporting rate for CD4 counts declined to 78.4% for cohorts on treatment for 30 months and to 59.8% for those in the cohorts reaching 42 months of ART.

There was a significant difference in the percentage of patients with CD4 counts > 200 cells /mm^3 between the 6 month cohort (62.5%) and the 30 month cohort (90.1%) in which the proportion peaked. Cohorts on ART for durations longer than 30 months had a lower proportion of patients with a CD4 > 200 cells/mm^3, however the difference was not statistically significant.

Table 7: Viral load results for adults on ART

Duration of treatment	Number of viral loads reported in ART register	VL completion (no. of viral loads reported / no of patients on treatment)	% VL suppressed (<400 copies/ml)
Months	No.	%	% & 95% CI's
3	2581	35.2%	89.7% (86.1% to 93.4%)
6	4614	85.8%	90.7% (87.9% to 93.5%)
12	2393	86.4%	89.4% (85.6% to 93.3%)
18	934	85.5%	87.3% (81.4% to 93.5%)
24	414	83.5%	87.9% (79.1% to 97.4%)
30	244	82.4%	85.2% (74.1% to 97.7%)
36	138	75.8%	86.2% (71.4% to 103.2%)
42	58	59.8%	86.2% (63.9% to 113.7%)
48	20	46.5%	90.0% (53.3% to 142.2%)

Figure 5: Viral load results for adults on ART



The trend in capturing viral load results in the register followed the same patterns as CD4 counts with a reduction of viral load results reported amongst the cohorts who had been on treatment for longer than 30 months. The percentage of patients with viral loads < 400 copies/ml was highest amongst

the 6 month cohorts (90.7%) and remained consistent at 85 % to 90% in cohorts on ART for longer durations.

3. Temporal trends

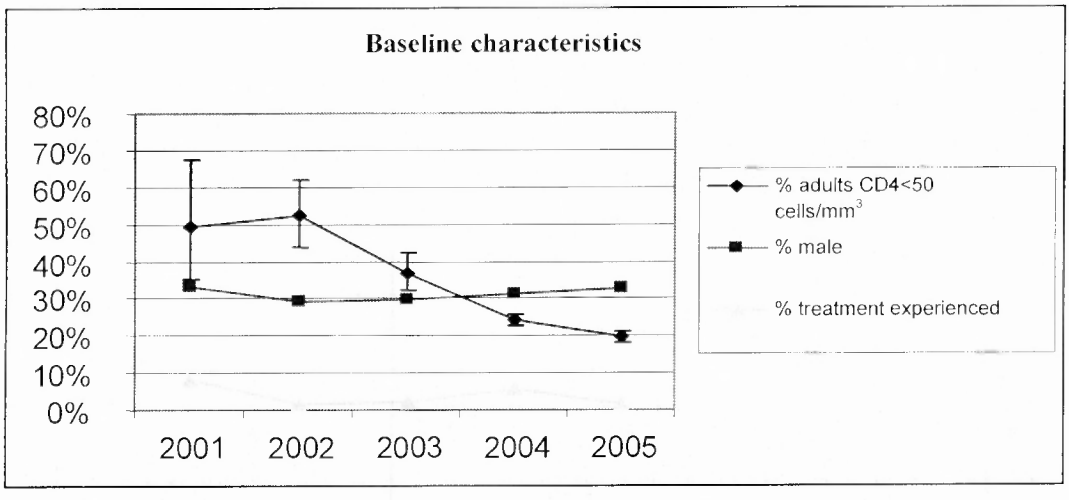
The number of patients enrolled annually increased from 81 in 2001 to 4167 in 2004. In the first 6 months of 2005 3619 patients were recruited.

3.1 Baseline trends

Table 8: Baseline trends for adults on ART

		2001	2002	2003	2004	2005
No. of patients on ART		81	255	576	4167	3619
% of patients starting ART with CD4 <50 cells/mm^3	**%**	49.4%	52.2%	37.0%	24.0%	19.7%
	95% CI	35.3 to 67.2%	43.7 to 61.8%	32.2 to 42.3%	22.5 to 25.5%	18.3 to 21.2%
Males	**%**	33.3%	29.4%	29.9%	31.2%	32.7%
Treatment experienced	**%**	8.0%	1.5%	2.2%	5.6%	1.5%

Figure 6: Temporal trends in baseline characteristics trends for adults on ART



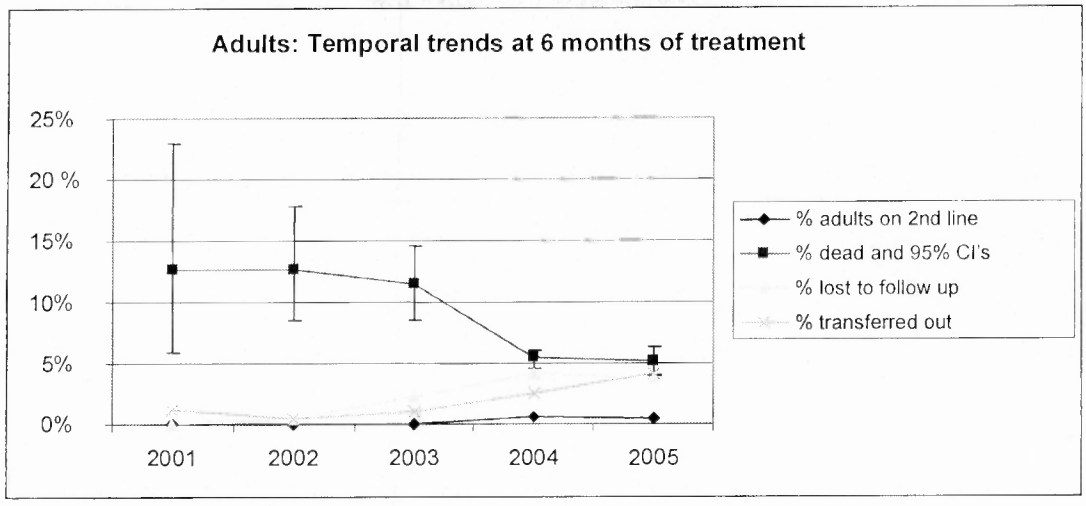
There was a significant decrease in the proportion of patients with a baseline CD4 count < 50 cells/mm^3 from 2001 (49.4 %) to 2005 (19.7%). The percentage of male patients enrolled was fairly consistent ranging between 29% and 34%. The percentage of patients with prior exposure to ART was highest for those in the 2001 cohort (8%).

3.2 Temporal trends at 6 months

Table 9: Temporal trends at 6 months in adults on ART

Outcomes at 6 months	2001	2002	2003	2004	2005
Number of patients started on treatment in year	80	247	515	3892	1574
On second line at 6 months	0	0	0	0.57%	0.51%
Cumulative deaths for period 0 to 6 months	10(12.7%)	31(12.6%)	58(11.4%	204(5.4%)	79(5.2%)
95% CI for cumulative % deaths for period 0 to 6 months	5.9 to 29%	8.5 to 17.8%	8.5 to 14.6 %	4.5 to 6.0%	3.9 to 6.3%
Remaining in care but stopped ART	3	5	12	67	33
Patients lost to follow up for period 0 to 6 months	0	1	11	159	57
Patients transferred out in period 0 to 6 months	1	1	5	95	65
Remaining in care at 6 months	87.3%	87.0%	86.5%	90.4%	91.0%
Percentage of patients in care with a CD4 reported at 6 months	100.0%	94.3%	93.2%	89.3%	74.5%
Percentage of these CD4's >200	51.5%	51.3%	58.7%	62.7%	66.2%
VL completion% at 6 months	100.0%	95.7%	92.6%	88.4%	74.7%
Percentage of these viral loads < 400 copies/ml	87.9%	90.1%	94.2%	89.8%	92.5%

Figure 7: Temporal trends at 6 months in adults on ART



The percentage of patients on second line ART at 6 months remained low (<1%). The percentage of patients dead by 6 months of ART decreased significantly from the 2003 cohort (11.4%) to 2004 cohort (5.4%) and stabilized in the 2005 cohort (5.2%). The percentage of patients lost to follow up was higher amongst the 2004 and 2005 cohorts; however the rate was consistently low (<5%).

Figure 8: Temporal trends in the reporting of CD4 and viral load at 6 months

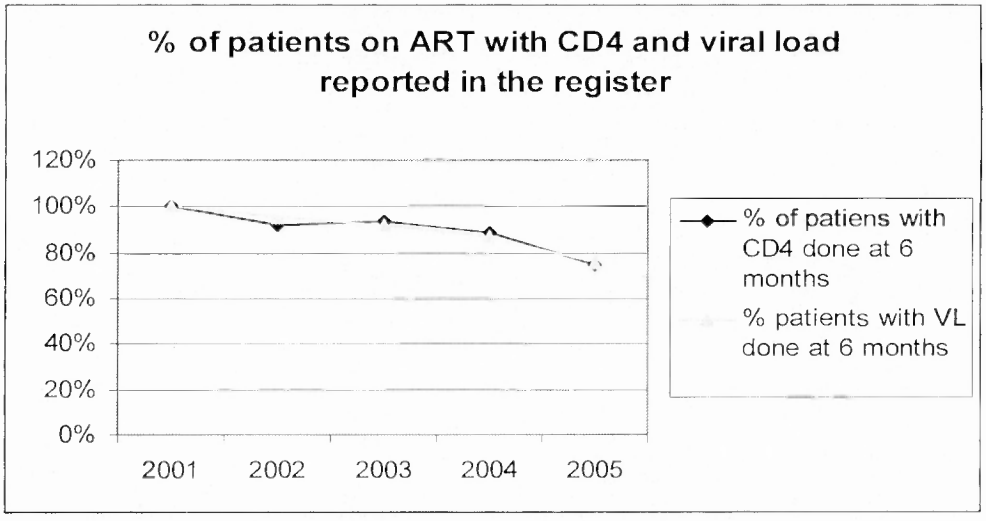


Figure 8 shows the decline in the percentage of viral loads and CD4 counts reported in the register. The reporting rate dropped to < 80% in the 2005 cohort.

Figure 9: Temporal trends in the results of CD4 and viral load tests at 6 months

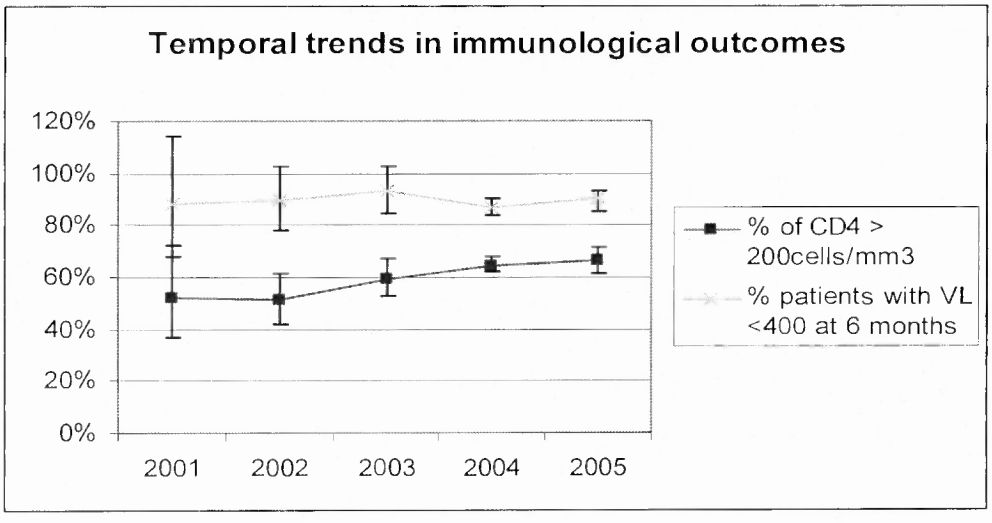


Figure 9 shows a significant increase in the percentage of patients with a CD4 > 200 cells/mm^3 at 6 months in cohorts from 2001(51%) to 2005 (66.2%). The

percentage of patients with viral load < 400 copies/ml remained stable over the consecutive cohorts ranging from 87% to 92%. These increases were not statistically significant.

4. Determinants of mortality

The unadjusted incidence rate ratio of death at 6 months for a 10% increase in the proportion of adults with a CD4 count < 50 cells/mm^3 (CD50prop) was 1.28 (95% CI's = 1.191 to 1.3). The fit of this regression model was highly significant (P < 0.001).

Table 10: The effect of year on the IRR of death at 6 months

Year of starting treatment	IRR	P	95% confidence interval
year2001	2.2	0.016	1.2 to 4.3
year2002	2.4	0.000	1.6 to 3.6
year2003	2.0	0.000	1.5 to 2.8
Year2004	1		
year2005	1.1	0.704	0.8 to 1.4

Table 10 shows that the unadjusted incidence rate ratio for death increased if patients were started on treatment prior to 2004.

In addition regression analysis showed that the unadjusted effect of region on the incidence of death at 6 months was not significant (p>0.05).

Table 11: Incidence rate ratios for the effect of independent variables on cumulative death at 6 months showing the Poisson regression models assessed

Model	Independent variables	IRR	P	95% CI	Wald chi squared	Lrtest alpha	Lrtest for model
Model 1	CD50prop	1.0275	0.000	1.019 to 1.036	0.000	0.000	
Model 2	CD50prop	1.0265	0.000	1.018 to 1.035	0.000	0.000	0.1975
	Menprop	1.008	0.195	0.996 to 1.021			
Model 3	CD50prop	1.021	0.000	1.010 to 1.031	0.000	0.000	0.0519
	Menprop	1.008	1.19	0.996 to 1.021			
	year2001	1.456	0.288	.728 to 2.909			
	year2002	1.459	0.124	.901 to 2.362			
	year2003	1.693	0.002	1.205 to 2.379			
	Year2004	1					
	year2005	1.017	0.913	0.753 to 1.373			
Model 4	CD50prop	1.021	0.000	1.011 to 1.031	0.000	0.007	0.0151
	Menprop	1.007	0.251	0.995 to 1.020			
	year2001	1.526	0.232	0.763 to 3.053			
	year2002	1.537	0.081	0.948 t0 2.491			
	year2003	1.807	0.001	1.281 to 2.548			
	Year2004	1					
	year2005	0.973	0.858	0.721 to 1.313			
	The Metro	1					
	Boland Overberg	2.435	0.016	1.183 to 5.012			
	South Cape	2.195	0.01	1.202 to 4.007			
	West Coast Winelands	2.061	0.034	1.057 to 4.020			

Definitions for abbreviations in table 11:
*CD50prop: Proportion of patients with a CD$ count < 50 cells/mm^3 at the start of ART,
*Menprop: Proportion of adults wo were men
*Year#### = year in which patients started ART

Multivariate Poisson regression was used to look at the effect of baseline characteristics on the proportion of patients dead at 6 months.

The full model included 4 independent variables:

a) CD50prop

b) The percentage of patients enrolled who are men

c) Year of starting treatment

d) The geographical region of the clinic where ART was provided

The decision to include dependent variables was based primarily on their epidemiological importance. The statistical significance of the inclusion of baseline variables in the model was assessed using log likelihood ratios (lrtest). The final model was found to have a significant goodness of fit (P <0.001).

Aggregation of data necessitated the use of proportions e.g. percentage men and CD50prop. Year of starting treatment and region were categorical variables. In these categorical variables dummy variables were generated. In the final model 2004 and Metro were used as the reference variables for year and region respectively. These two reference categories were chosen as they were the categories with the biggest sample size.

Table 11 describes the results of each model. In the final model the IRR for CD50prop was 1.02, signifying a 2% increase in the incidence rate of death at 6 months for each 1% increase in cd50prop. This effect was significant (P <0.001). Being started on treatment in 2003 leads to a 1.8 times increase in the rate of death at 6 months compared to being started in 2004. This effect was also highly significant (P <0.001). Being treated in a region other than the Metro led to an increase in the death rate at 6 months of ART, when compared to all 3 other regions. This effect was statistically significant in all cases. The model showed a significant degree of variance between facilities in the death at 6 months (lrtest alpha=0, P = 0.007).

Results

B. Children

This report covers 81.6% of children started on ART from January 2001 till the end of July 2005. The data on the remaining children on ART is not included as a result of non-reporting by facilities.

1. Baseline cohort data, 1 January 2001 to 31 July 2005

Of the 1271 children captured by the monitoring system during this period, 38.9% had a CD4 count less than 50 cells/mm^3 and 12.2 % were treatment experienced. The sex of children is not recorded in the ART register.

2. Longitudinal trends

Figure 10: Trends in the number of children in treatment in July 2005

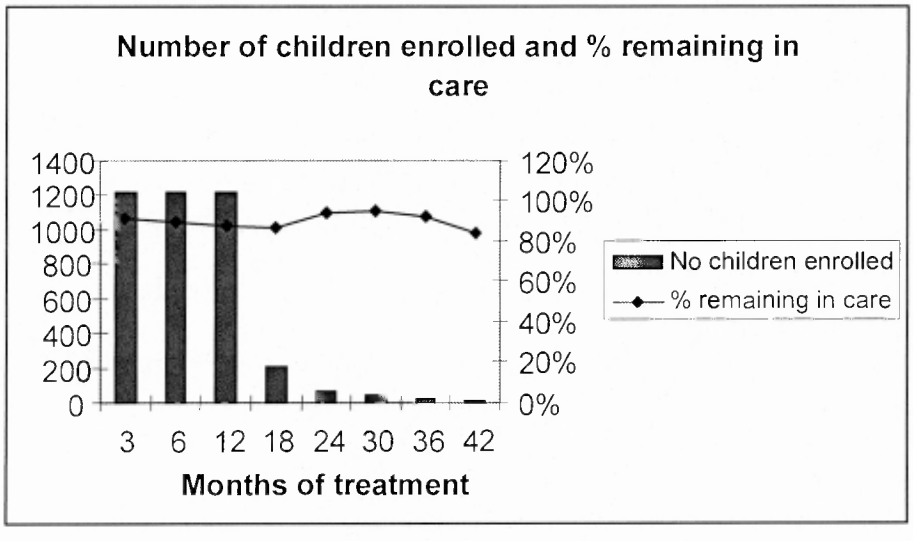


Figure 10 illustrates the decreasing number of patients at increasing durations of treatment at the end of July 2005. As shown, most children in the

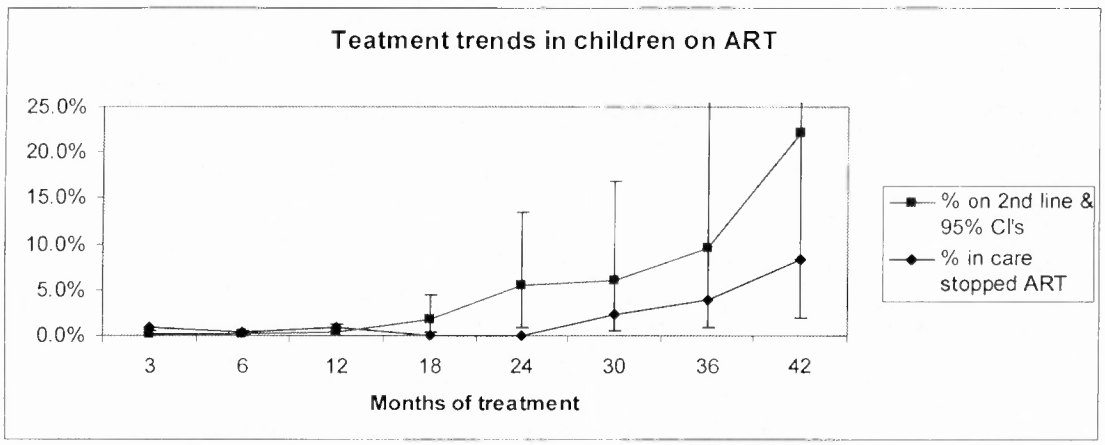
programme had been started on treatment in the preceding 12 months. The percentage remaining in care is > 80% at all times.

2.1. Treatment trends

Table 12: Trends in treatment in children on ART

Duration on ART	Total patients	Percentage children on 2nd line	Percentage children still in care but stopped ART
Months	No	% & 95% CI	%
3	1218	0.1% (0.0% to 0.5%)	0.8%
6	941	0.1% (0.0% to 0.6%)	0.4%
12	582	0.4% (0.0% to 1.2%)	0.9%
18	201	1.8% (0.3% to 4.4%)	0.0%
24	65	5.5% (0.9% to 13.5%)	0.0%
30	43	6.1% (0.6% to 16.8%)	2.3%
36	26	9.5% (0.9% to 27.8%)	3.8%
42	12	22.2% (2.0% to 60.2%)	8.3%

Figure11: Percentage of children on second line and in care but stopped ART



The percentage of children on second line treatment increased amongst cohorts on ART for longer durations, particularly in those on treatment for longer than 18 months. Small sample sizes limited the interpretation of this trend.

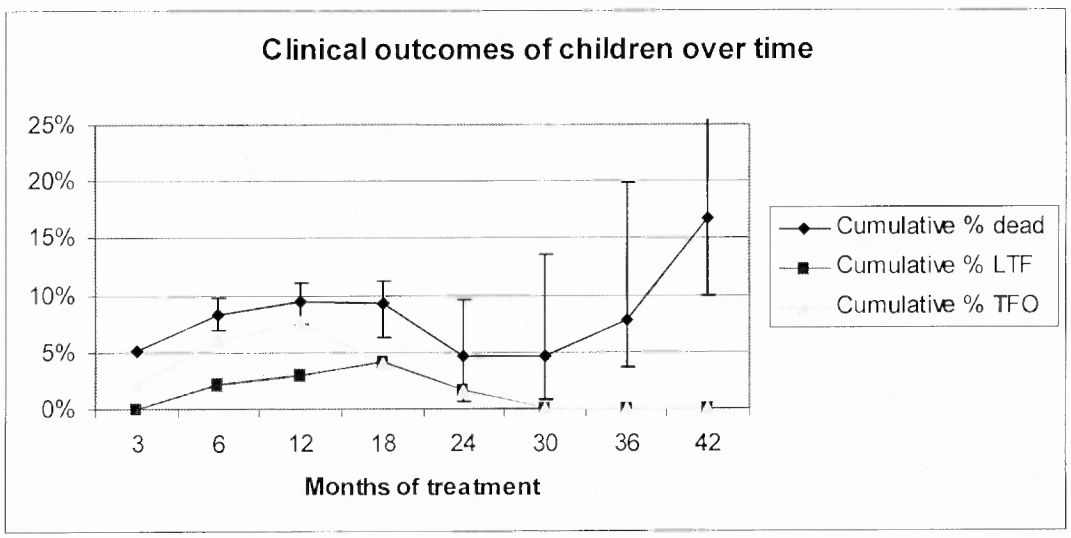
The percentage of children in care, but no longer on ART similarly remained low (<4%) until after 42 months of ART. Once again the small sample size (n<70) was reflected by the poor precision of this estimate.

2.2. Death, loss to follow up and transfer out

Table 13: Death, loss to follow up and transfer out of children on ART by duration of treatment

Duration of treatment	Initial total	Cumulative percentage children dead	Percentage children remaining in care	Percentage children lost to follow up	Percentage children transferred out
Months	No.	% & 95%CI	%	%	%
3	1218	5.2% (4.0% to 6.7%)	92.7%	0.0%	2.1%
6	941	8.2% (6.1% to 9.8%)	89.6%	2.1%	5.9%
12	582	9.5% (6.5% to 11.5%)	87.5%	3.0%	7.6%
18	201	9.3% (5.3% to 14.2%)	86.5%	4.1%	4.0%
24	65	4.7% (0.9% to 13.5%)	93.8%	1.6%	1.5%
30	43	4.7% (0.6% to 16.8%)	95.3%	0.0%	0.0%
36	26	7.7% (0.9% to 27.8%)	92.3%	0.0%	0.0%
42	12	16.7% (2.0% to 60.2%)	83.3%	0.0%	0.0%

Figure 12: Death, loss to follow up and transfer out of children on ART



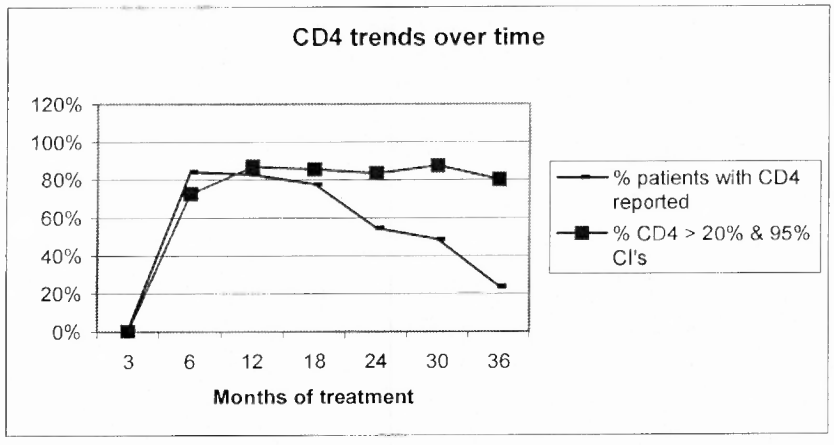
The cumulative percentage of children dead peaked in the 12 month cohorts (9.5%) and then dipped to 5 % in the 36 month cohorts, however this change was not statistically significant. The percentage of patients lost to follow up peaked amongst the 18 month cohort (4.1%) and then decreased in subsequent cohorts. There was no loss to follow up amongst those patients still on ART after 30 months. The percentage of patients transferred out was highest amongst those patients at 12 months of ART (7.6%).

2.3. Immunological outcomes

Table 14: CD4 results for children on ART

Duration	CD4's reported in the ART register	Percentage CD4 completed (CD4 reported/ patients on ART)	Percentage CD4 counts > 20 % (CD4 > 20%/ CD4 reported in ART register)
Months	**Total**	**%**	**% & 95% CI's**
3	11	1.0%	0.0% (0.0% to 0.0%)
6	663	84.2%	72.4% (66.1% to 79.2%)
12	385	82.6%	86.8% (77.7% to 96.6%)
18	131	77.5%	85.5% (70.4% to 102.9%)
24	30	54.5%	83.3% (53.9% to 123.0%)
30	16	48.5%	87.5% (47.8% to 146.8%)
36	5	23.8%	80.0% (21.8% to 204.8%)

Figure 13: CD4 results for children on ART

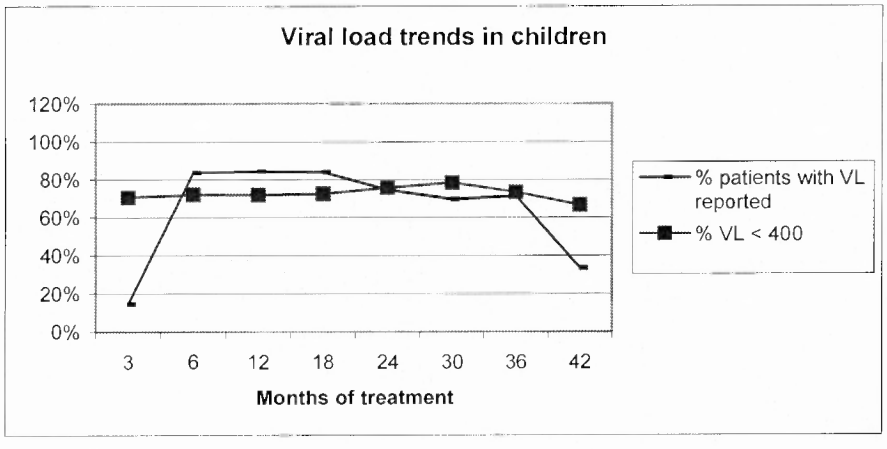


Patients routinely have their first on-treatment CD4 count done at 6 months. Reporting of blood test dropped in cohorts on treatment for longer than 18 months; the reasons for this are unclear and are under investigation. The percentage of children with a CD4 count > 20% is 86.8% in the 12 month cohorts and remained stable amongst cohorts of patients on ART for durations up to 36 months.

Table 15: Viral load results for children on ART

Duration	Viral loads done	VL completion%	VL supp%	
Months	**Total**	**%**	**%**	**95% CI**
3	160	14.5%	70.6%	58.2% to 84.9%
6	658	83.6%	72.0%	65.7% to 78.8%
12	393	84.3%	71.8%	63.6% to 80.6%
18	142	84.0%	72.5%	59.2% to 87.9%
24	41	74.5%	75.6%	51.4% to 107.3%
30	23	69.7%	78.3%	46.4% to 123.7%
36	15	71.4%	73.3%	36.7% to 131.2%
42	3	33.3%	66.7%	8.1% to 240.7%

Figure 14: Viral load results for children on ART



The data shows the durability of ART in children. Viral load suppression rates peaked at 78.5% in the 30 month cohorts with a non significant decrease in

subsequent cohorts. The reporting rate for viral loads dropped in the cohorts reaching 42 months of ART.

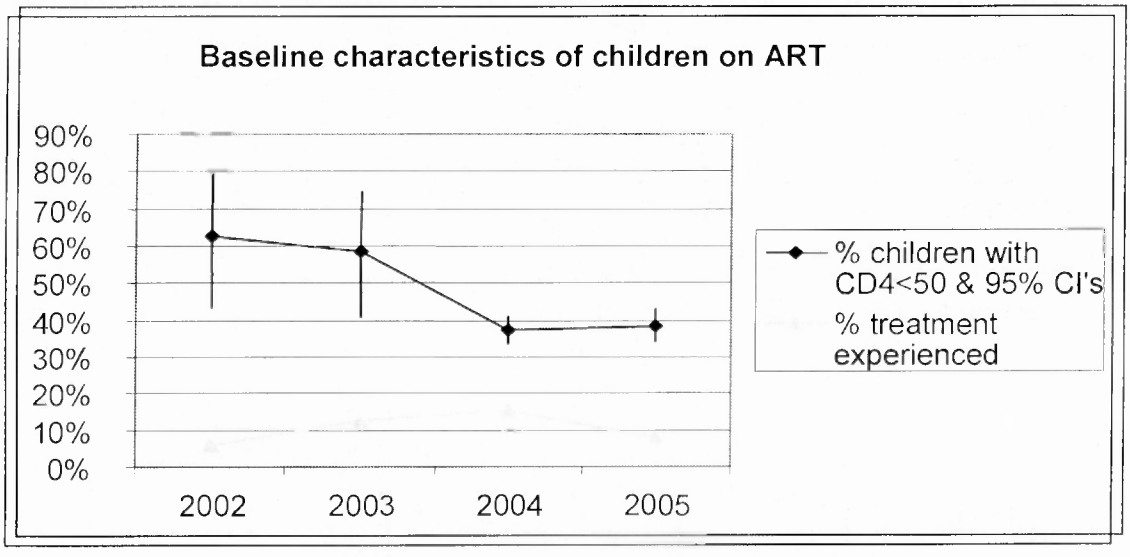
3. Temporal trends

3.1. Baseline trends

Table 16: Baseline trends for children on ART

	2002	2003	2004	2005
Total number of children enrolled	32	36	737	462
Percentage with CD<50 cells/mm^3	62.5%	58.3%	37.2%	38.5%
Percentage treatment experienced	5.9%	12.2%	15.0%	7.8%

Figure 15: Baseline trends for children on ART



The data for 2001 is not presented here as the sample size was too small for meaningful comparison. There was a significant drop in the proportion of children with a baseline CD4 count < 50 cells/mm^3 from the 2003 cohorts

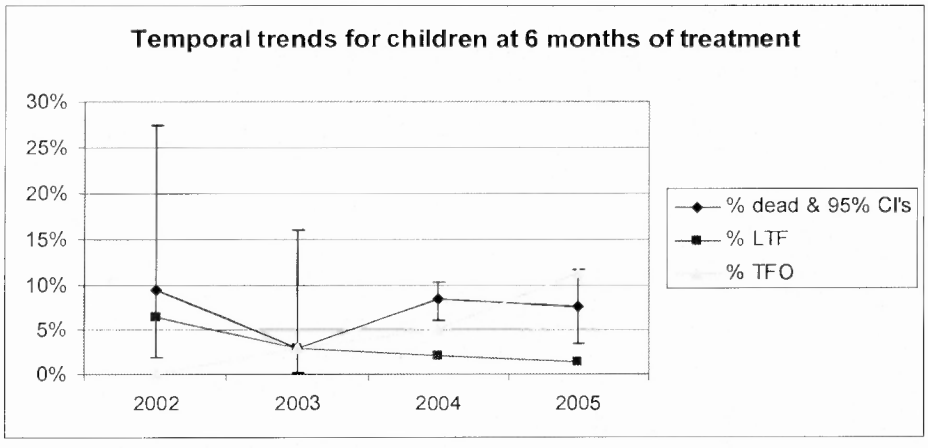
(58.3%) to 2004 cohorts (37.2%) and through 2005. There is no clear trend in the percentage of children who are treatment experienced.

3.2. Temporal trends

Table 17: Temporal trends in specified outcomes at 6 months for children on ART

Outcomes	2001	2002	2003	2004	2005
Number of patients started on treatment in year	4	32	35	697	177
On first line at 6 months	3	29	33	584	141
On second line at 6 months	0	0	0	1	0
In care but stopped ART at 6 months	0	1	1	1	1
Cumulative deaths for period 0 to 6 months	1	3	1	56	12
Cumulative %deaths for period 0 to 6 months	25.0%	9.4%	2.9%	8.5%	7.6%
95% confidence intervals for cumulative % deaths for period 0 to 6 months	0.6 to 139.3%	1.9 to 27.4%	0.1 to 16.0%	6.1 to 10.4%	3.5 to 11.8%
Patients lost to follow up for period 0 to 6 months	0.0%	6.3%	2.9%	2.1%	1.3%
Patients transferred out in period 0 to 6 months	0.0%	0.0%	2.9%	5.0%	11.3%
Remaining in care at 6 months	75.0%	84.4%	94.1%	89.4%	91.1%

Figure 16: Temporal trends in death, loss to follow up and transfer out at 6 months for children on ART

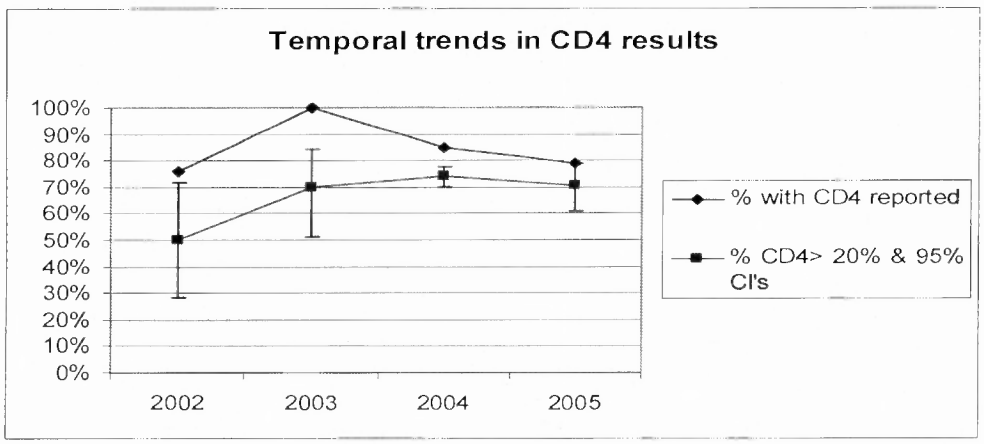


The cumulative percentage of children dead by 6 months dipped to 2.9% in the 2003 cohorts. The percentage dead at this duration of ART in the 2004 cohort was 8.5%. The percentage of patients lost to follow up was low and the temporal trend was toward a reduced rate; decreasing from 6.3% in 2003 to 2.9% in 2004. The number of patients transferred out increased from 2.9% in 2003 to 11.3% in 2005.

Table 18: Temporal trends in immunological outcomes in children on ART at 6 months of treatment

Immunological outcomes	2001	2002	2003	2004	2005
CD4 completed at 6 months	100.0%	75.9%	100.0%	85.0%	79.4%
Percentage of these CD4's >20%	66.7%	50.0%	69.7%	74.0%	67.9%
95 % CI for % of CD4 > 20%		28.2% to 71.8%	51.3 to 84.4%	69.9 to 77.8%	60.8 to 78.8%
VL completion% at 6 months	100.0%	89.7%	84.8%	82.4%	87.2%
Percentage of these viral loads < 400 copies/ml	100.0%	88.5%	82.1%	69.7%	74.8%
95 % CI's for % of viral loads < 400 copies/ml		69.80 to 97.6%	63.1 to 93.9%	65.4 to 73.8%	66.0 to 82.3%

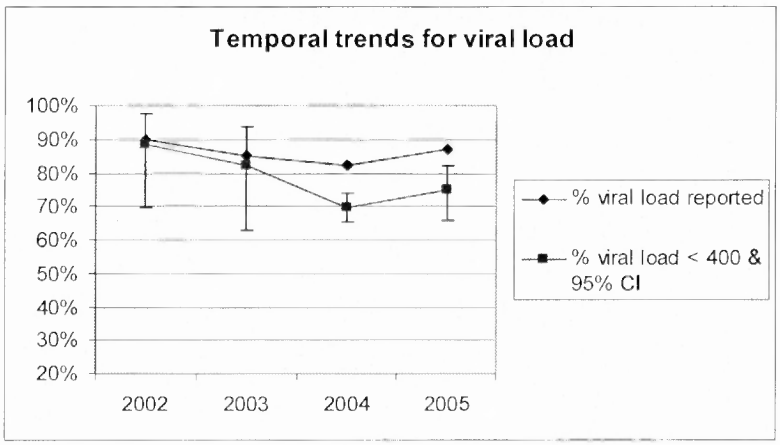
Figure17: Temporal trends in CD4 counts in children on ART at 6 months of treatment



The percentage of children in care with a CD4 count reported declined from 2003 (100%) to 2005 (79.4%). The percentage with a CD4 > 20% at 6 months

increased from 2002 (69.7%) to 2003 (74.0%) and dropped slightly in 2005 (70.4%). These changes in CD4 count values are not statistically significant.

Figure18: Temporal trends in viral loads in children at 6 months



The percentage of children with viral loads reported at 6 month ranges from 80 to 90%; the lowest reported rate was in 2004 (82.4%). The number of children with viral load suppression at 6 months of treatment was highest in the 2002 cohorts (88.5%) and lowest in the 2004 cohorts (69.7%). However, this difference was not statistically significant. The viral load suppression rate increased again in the 2005 cohorts reported thus far (74.8%).

4. Determinants of mortality

As with the adult data Poisson regression was performed using the IRR of death by 6 months of ART as the dependent variable and CD50prop, year of starting ART and region as independent variables.

There was no data for children on treatment in the Boland / Overberg due to a failure by these sites to report on the children in their care. Dummy variables were created for region and year, with 2004 and the Metro region being

chosen as reference categories as they had the largest number of patients. Data from 2001 was excluded from analysis because of the small sample size (n = 4).

In a model with only CD50prop included as an independent variable and death at 6 months as the dependent variable, the CD50prop had a borderline unadjusted effect on the incidence rate ratio for death at 6 months (IRR=1.017 P= 0.064 95% CI's 0.99 to 1.35). This means that a 1% increase in the percentage of children with CD4 < 20% leads to a 1.017 times increase in the rate of death at 6 months of ART although this association was only of borderline significance (P>0.05). The fit of the model was borderline but not statistically significant (P=0.064).

A model with CD50prop as the dependent variable and region included as the independent variable showed that if a child was on treatment in the South Cape s/he was 64.5% less likely to have a baseline CD4 count < 50 cells/mm^3. This effect was highly significant (IRR 0 .36 P=0.001 95% CI's = 0.195 to 0.649). The fit of this model was also highly significant (P=0.001). No significant correlation was found between year of starting ART and CD50prop.

Multivariate Poisson regression models measuring the effect of dependent variables on the IRR of death at 6 months did not significantly alter the effect of CD50prop on the IRR at 6 months. The fit of these models was poor and for this reason they are not presented here.

Discussion

A. Discussion of data (adults and children)

The data confirms a rapid scaling up of the ART programme in the Western Cape between April 2004 and July 2005, with an increase in the total patients on treatment of 2339 to 10478. The desired study sample included data on all patients on ART in the public service; however, the reporting rate was limited to 97.5% for adults and 81.6% for children. The reason for this missing data was a failure of some sites to provide complete, valid quarterly reports.

1. Longitudinal trends

The results of the adult data showed high rates of patient retention (>80%). The rate of patients leaving the programme was highest during the first 18 months of ART; after this duration of treatment the percentage remaining in care was stable above 80%. This trend most likely reflects the higher mortality rates during the initial treatment period as well as the fact that those patients still in care after 18 months are unlikely to subsequently default. The cumulative death rate for adults peaked amongst those patients in the 30 month cohorts (16%). Longitudinal trends for children were similar to those observed in the adult data with overall better patient retention. The death rates were lower (<10%) than in adults and peaked earlier at 12 months of ART; however the 95% confidence intervals around the point estimates for death rates were not mutually exclusive.

The rate of loss to follow up was consistently low in the adult data, peaking at 6.0% in the 12 month cohorts and then decreasing amongst the cohorts on ART for longer durations. The patients represented by the data for durations greater than 24 months were treated almost exclusively at donor assisted sites, and therefore this better retention of patients may reflect the better quality care delivered at these more resourced clinics. For example, the clinics supported by the Desmond Tutu Foundation had a significantly higher number of ART counselors than clinics supported exclusively by the state. The percentage of children lost to follow up was less than in adults, peaking at less than 5% amongst those children on ART for 18 months. Although the rates reported here for both adults and children are favourable, the reasons for loss to follow up should be reviewed continuously.

The rate of reporting of routine blood test results was lower (<85%) than other reported indicators and decreased dramatically in both adults and children for those patients on treatment for more than 36 months. This is highly significant programmatically, as it may reflect a failure by clinicians to continue with immunological monitoring once patients are stable on treatment, and therefore warrants further investigation.

The immunological markers reported show the positive effect of ART on the patients' immune systems and the durability of this effect. In both adults and children, the greatest increase in the proportion of patients with a CD4 count > 200 cells /mm^3 / 20% occurred in the first 12 months of treatment. This

increase in the proportion of CD4 counts > 200 cells /mm^3 / 20% showed no significant increase or decrease after 12 months of treatment.

Viral load suppression rates were high amongst adults (>85%) and children (>70%). The major reduction in viral load was achieved in the first 3 months of ART with no significant increase in suppression rates after this duration.

The results from the adult data on longitudinal outcomes were very similar to published South African and international studies and appear to confirm the belief, expressed by Laurent et al, that the largely treatment naive population of Sub Saharan Africa will fare well on ART and exhibit adequate adherence. It should also be noted that the previously published South African studies were conducted at donor assisted sites; whereas the data in this report is from all ART sites, the majority of which are purely state funded [18, 19, 29-31].

The data from international studies reviewed in this paper produced marginally higher rates of viral load suppression. However this difference must be viewed in the context of the baseline differences in patient and contextual factors experienced in ART programs in resource-poor settings. This comparison is discussed in the ART-LINC study [22], where they show that after adjusting for baseline characteristics the treatment success rates after 6 months of ART between adult cohorts from developed and developing countries were not statistically different However the study did not adequately address the higher rates of loss to follow up amongst the cohorts from developing countries as patients lost to follow up were excluded from

analyses. Intention to treat analysis would most likely have lead to higher hazard ratios amongst patients in the developing world [20].

The data on children analysed in this paper compared very favourably with published data. Fassinou et al from the Ivory Coast reported survival rates of 91% at 12 months in their cohort. These results are marginally higher than this data, which reports 87.5% of children still in care at this duration of ART. This difference was not statistically significant [25].

2. Temporal trends

The number of adults and children enrolled for ART increased yearly, with 81 adults and 6 children being enrolled in 2001 and 4167 adults and 737 children in 2004.

There was a significant reduction in the proportion of patients with a baseline CD4 count < 50 cells/mm^3 from 2003 (37%) through 2004 (24%), to 2005 (19.7%). This trend was also observed in the paediatric data with the proportion of children with a CD4 count < 50 cells/mm^3 decreasing from 58.3% in 2003 to 37.2% in 2004. The decline in baseline CD4 count can be seen to reflect the scaling up of the treatment programme and the earlier enrolment of healthier patients onto ART [19].

Approximately 30% of the adults enrolled for ART were men. This trend is in keeping with other published studies and reflects the widely reported

phenomenon that uptake into treatment for HIV amongst men in Sub Saharan Africa is low. It also reflects the higher recruitment of women onto ART through the PMTCT programme [18, 19].

The proportion of treatment experienced adult patients peaked in the 2001 cohorts at 8% and remained < 6% amongst subsequent cohorts. The rates in children were higher peaking at 15% in the 2004 cohorts. The association of treatment experience to an increased risk of resistance to ART makes monitoring of this trend vital. The high proportions of treatment experienced patients, particularly in children, may reflect the transfer in of patients from the private sector and research programmes [13, 19, 22].

The proportion of adults dying in the first 6 months of ART decreased significantly from 2003 (11.4%) to 2004 (5.4%) and 2005 (5.2%). The decreased rate of deaths in 2004 and 2005 cohorts may reflect the improvement in the baseline health of patients starting ART as well as the improved delivery of ART that occurred with the start of the rollout. The 6 month death rates in children did not exhibit the same trend with 2.9% dead by 6 months amongst the 2003 cohorts and 8.5% amongst the 2004 cohorts. This trend may reflect a reduction in the standard of care as children are transferred out from specialist sites and research programmes to primary health care facilities. The death rates for children at 6 months for all years reported were not statistically different from those of adult patients.

The data showed an increase in loss to follow up at 6 months amongst adults from 5% in 2004 to 11.3% in 2005. The rate was lower in the paediatric data, 2.1% in 2004 and 1.3% in 2005. The longitudinal data showed that the highest rates of loss to follow up occurred after 18 months of treatment. This peak will therefore not be reflected in this analysis.

The above rates of loss to follow up are an important consideration for the Provincial Department of Health when considering future models of care for treating patients with HIV / AIDS. Similarly the role of the community health worker will need to be reviewed as they are seen to be vital in the promotion and monitoring of adherence to ART [19].

There was an increase in the rate of transfer out of patients including down referral from secondary and tertiary hospitals to primary care sites during the first 6 months of ART, reaching 4.1% in adults and 11% in children in the 2005 cohorts. This reflects the scaling up of the programme and the opening up of new clinics.

The number of adults and children on second line treatment at 6 months remained low (< 1%) and showed little variation between the cohorts from 2002 to 2005. As shown in the longitudinal data, the major increase in the number of patients on second line treatment occurred after 18 months and is therefore once again not reflected in this analysis.

There was a rise in the percentage of adult patients with a CD4 count > 200 cells/mm^3 at 6 months from 2002 to 2005, although this rise was not significant. The paediatric data showed a similar temporal trend with a lower peak of 74% amongst the 2004 cohorts. This trend may partially reflect an improvement in baseline characteristics. The proportion of adults with a viral load < 400 copies/ml at 6 months increased from 87% in 2001 to 93% in 2005. This outcome reflects very positively on the ART programme in the Western Cape. In contrast there was a non-significant decline in the rate of viral load suppression at 6 months amongst children in the 2004 cohorts. This may once again reflect the shift from tertiary to primary care.

2.1 Explanation of the temporal trends in adults and children

The temporal trends described for adults and children reflect multifactorial changes in the provision of ART over recent years. Phillips et al [32] pointed out that ART treatment has only been widely available for less than 5 years, during which time there have been many changes in its provision. These changes have been multilevel, affecting both the patients enrolling for ART and the delivery of the service. The authors suggested that the temporal trends were therefore difficult to explain and should be the subject of ongoing analysis and research. Changes in the provision of ART from 2001 to 2005 in the Western Cape can be categorised as follows:

a) Patient factors

These are reflected in the data. The decrease in the proportion of patients with a baseline CD4 < 50 cells/mm^3 was the most significant of these and reflected the scaling up of the service, as the earlier cohorts constituted only the sickest patients. This confirms the trend reflected in the paper by Bekker et al [19]. Having a baseline CD4 count < 50 cells/mm^3 was shown to increase the incidence rate of death by 6 months in the adult data.

The current approach to promoting adherence to ART in South Africa is to maximise patient knowledge through an extensive workup period, which includes group counselling, home visits, and multi-disciplinary assessments of patient readiness. This process encourages adherence by enhancing patient autonomy; it represents a step away from the Directly Observed Treatment (DOTS) approach used by the tuberculosis programme and embraces the principles of patient centered medicine contained in the Primary Health Care approach.

There is increasing interest in the effect of the stigma around HIV / AIDS on the willingness of patients to enter into HIV treatment and to continue with it. The rollout of ART is thought to have reduced the stigma surrounding HIV in the Western Cape as HIV /AIDS is no longer seen as a 'death sentence'. This may be a significant factor in the improved willingness of patients to disclose their status and enter into treatment in years to come [33].

b) Health care factors

The expansion of the ART service since April 2004 has been dramatic with the total number of adults recruited in 2004 reaching 4167 and the number of sites increasing from 20 to 37 by July 2005. In addition there has been a move from more resourced donor-assisted clinics, to a larger number of clinics run exclusively by provincial staff. These staff have often had less experience working with ART and there are also fewer resources available for all aspects of patient care.

The first clinics were all located in the Metro region. With the scaling up of the service, ART facilities have been opened in all four regions. This expansion has improved the equity of the ART service; however there are still many areas where no ART clinic is easily accessible. Regression analysis of the adult data has shown that being treated in a region other than the Metro was found to significantly increase the incidence of death by 6 months of ART, suggesting higher standards of care in the Metro.

As the availability of ART in an area is established, one would expect patients being enrolled onto treatment to be healthier with higher baseline CD4 counts. However regression analysis in this study shows that children starting treatment in the South Cape / Karoo are significantly less likely to have a CD4 count less than 50 cells /mm^3 at baseline. This suggests better access to ART services in this region. This, however, is not the case; the higher baseline CD4 count must therefore reflect other patient/contextual factors in this region.

This analysis therefore shows that researchers should be cautious about using baseline CD4 count as a proxy measure of access to treatment.

The scientific knowledge around ART is constantly improving and must also be considered as a dynamic factor affecting treatment outcomes.

3. Determinants of mortality in adults and children

The data showed that a 10% increase in the proportion of patients with a CD4 count < 50 cells/mm^3 at baseline lead to an IRR of 1.2 for death at 6 months of ART (P <0.001). This confirms an association already established in published literature [15, 19].

Patients treated in the Metro region were found to have significantly lower death rates at 6 months than those patients treated in other regions, viz. West Coast Winelands, South Cape / Karoo and Boland / Overberg.

This may be explained by the ways in which the Metro differs from other regions, as detailed below:

- Health facilities in the Metro are more accessible than in rural areas where greater distances must be covered to reach a clinic
- The number of patients on treatment in this region far outstrips that in other regions with better access to ART facilities staffed by more experienced health care professionals.
- Pilot treatment programmes have been running in the Metro since 2001

- There is greater availability of specialist input for ART patients in the Metro region

As discussed above baseline CD4 count was lower in the Metro than in other regions and the lower death rate at 6 months therefore most likely reflects health care factors than patient factors.

In children the unadjusted incidence rate ratio of death by 6 months of ART was 1.017 for patients with a baseline CD4 count < 50 cells/mm^3. This effect was of borderline significance (P=0.054). Further regression analysis was limited by sample size.

Limitations of the data provided by the current monitoring system

This study has provided useful insight into the strengths and weaknesses of the paper based ART monitoring system. Many of the problems commonly associated with routine data were encountered. Data problems data fall into two categories:

1. Missing data

As described earlier in the discussion of results, the reporting rate was 97.5% for adults and 81.6% for children. Data loss occurred at the following steps of the data collection pathway during:

- The patient visit, with filling in of patient information into the clinical record

- Transfer of data from the clinical records to the ART register
- Filling in and submission of the quarterly report
- Data aggregation and analysis

The reason for the poorer return on the paediatric data was that many of the paediatric sites were using self developed electronic databases.

The poor reporting of blood results was discussed earlier. This was most likely due to a failure to transcribe the results rather than a failure to do the test. One reason for this low reporting rate may be the time taken for the results to return from the laboratory to the ART facility. The delay makes the entering of the results into the register a retrospective, ad hoc process, in contrast to clinical information that can be entered on the day of the visit.

Data was not analysed on an intention to treat basis in this paper however lost to follow up is reported separately it is quite likely that a proportion of the LTF patients have died.

2. Poor quality data

Updating the ART register is time consuming and there is a shortage of facility based data staff to complete the task. In practice the job is often left to nursing or administrative staff, who have insufficient time to complete the task properly due to competing responsibilities.

The monitoring system design is complicated, making use of epidemiological concepts unfamiliar to most of the facility based staff. Although we have designed workshops and undertaken site visits to explain the system, there is still a worrying lack of understanding of the system. This problem has been exacerbated by rapid data staff turnover.

Site support remains the cornerstone for maintenance of the monitoring system. It has become evident that without data management staff from head office spending significant time at the sites, the reports are not completed correctly. This is a resource intensive task as the sites are spread throughout the Western Cape and at present the Provincial Department of Health does not have enough staff to provide adequate support.

In addition there are methodological problems inherent in the monitoring system:

- The breadth and depth of data in the quarterly report is limited. For example, the recording of adverse events relating to ART is captured by a parallel pharmacovigilance system.
- The categorical nature of the data collected has also limited analysis. For example, baseline CD4 count is either less than or greater than 50 cells/mm^3. This greatly limits subsequent analysis, such as calculating the mean increase in CD4 count over time.
- The aggregation of the data at facility level has also led to an inability to link baseline characteristics, e.g. CD4 count, to an individual event at a

given duration on ART. The aggregation of the data is very much part of the design of the paper system and a strong argument for the development and introduction of an electronic monitoring system, which will facilitate the recording of individual data and the subsequent integration of this data with other electronic data bases. The validity of the analysis will thus also be improved as aggregation leads to increased variance and error terms.

3. Future concerns

Although an electronic system recording individual level data remains the ultimate goal the current system has provided a good intermediate solution. Difficulties with obtaining reports have to date emerged mainly from sites using self-developed electronic systems which are not easily compatible with reporting requirements. The NDOH is committed to the implementation of an electronic monitoring system. This process has already begun with five clinics in the Metro region of the Western Cape having been cabled with internet access in the last 12 months.

The training of personnel has been a major focus in implementation of the paper based system. One must assume that the training requirements will increase if an electronic system is introduced especially in the initial period. The resources for data management in the province are limited and the expected impact of introducing an electronic system on these staff will need to be carefully considered.

The Western Cape DOH is currently piloting a new laboratory request form, which records more clinical data than presently captured. This will allow more meaningful interpretation of the CD4 and viral load results and is particularly desirable as the data in this report shows the manual recording of blood results is poor.

The current ad hoc system for capturing pharmacovigilance data is soon to be complemented by a more comprehensive sentinel surveillance system.

Recommendations

- Baseline data should be used to study baseline trends in patients enrolling into ART programs, to enable the most efficient allocation of health care resources. For example the enrolment of men could be prioritized through appropriate community based health promotion interventions.
- Outcome data should be used to set clinical care standards for facilities providing ART in keeping with the principles of clinical governance. Poorly performing facilities can thus be identified and the appropriate interventions implemented. Reports comparing death rates loss to follow up rates and viral load suppression rates (with 95% confidence intervals) can easily produced and will be a valuable tool for comparing quality of care at clinics. This analysis should form the basis for the completion of the clinical audit cycle which should be repeated at 12 monthly intervals.
- Development of a pharmacovigilance monitoring system needs to be prioritised to more effectively monitor side effects from ARV's.
- Lessons learnt in the use of the monitoring system outlined above need to be used to modify training of data personnel.

Conclusions

The monitoring system has provided vital information on patients on ART. The data generated confirms the feasibility of providing ART to both adults and children in the public health sector of the Western Cape Province and the durability of ART in this context.

The limitations of the current monitoring system have been discussed. If the monitoring system is to continue to be a useful tool for monitoring of clinical outcomes then these will have to be systematically addressed. As the ART programme expands there will be new challenges in both clinical care and the monitoring of patients.

Although there is a clear need for expanded reporting, the introduction of additional data elements to the current system and an electronic system will need to be undertaken cautiously as the potential exists for changes to bring a reduction in the quality of the data. These changes will need to be accompanied by the necessary scaling up of data staff at all levels of the monitoring and evaluation system in the province.

References

[1] Bradshaw D, Groenewald P, Laubscher R, Nannan N, Nojilana B, Norman R, et al. Initial burden of disease estimates for South Africa, 2000. South African medical journal 2003. Vol.93:682-8.

[2] World Health Organization. Epi update, HIV infection rates decreasing in several countries. Geneva, World Health Organization 2005.

[3] Joint United Nations Programme on HIV/AIDS. Epi update 2005, Fact sheet for Subsaharan Africa. Geneva, UNAIDS 2005.

[4] Joint United Nations Programme on HIV/AIDS. Methods and assumptions of HIV prevalence estimates. Geneva, UNAIDS 2007.

[5] Joint United Nations Programme on HIV/AIDS. About UNAIDS. Geneva, UNAIDS 2007.

[6] Provincial Government of the Western Cape. Voluntary Counseling and testing for HIV, Annual Report. Cape Town, Provincial Government of the Western Cape 2005.

[7] Provincial Government of the Western Cape. Western Cape Antenatal survey. Cape Town, Provincial Government of the Western Cape 2004.

[8] Statistics South Africa. Mid-year population estimates, South Africa. Pretoria, Statistics South Africa 2006.

[9] Medical Research Council SA. The impact of HIV AIDS on adult mortality in South Africa. Cape Town, Medical Research Council 2001.

[10] Department of Health of South Africa. Comprehensive HIV and AIDS Care, Management and Treatment Plan for South Africa. Pretoria, Department of Health of South Africa 2003.

[11] Provincial Government of the Western Cape. Antiretroviral Treatment Protocol Version 2. Cape Town, Provincial Government of the Western Cape 2004.

[12] Kwazulu Natal Department of Health. Psychosocial Support for Antiretroviral programmes. Durban, Kwazulu Natal Department of Health 2004.

[13] Ledergerber B, Opravil M, Telenti A, Hirschel B, Battegay M, Vernazza P, Sudre P, Flepp M, Furrer H, Francioli P, Weber R. Clinical progression and virological failure on highly active antiretroviral therapy in HIV1 patients a prospective cohort study. Lancet Infectious Diseases 1999. Vol. 353: 863-8.

[14] Chan KC, Hogg RS, Montaner JS, O'Shaughnessy MV. Survival rates after the initiation of antiretroviral therapy stratified by CD4 cell counts in two cohorts in Canada and the United States. AIDS 2002. Vol. 16: 1693-5.

[15] Schrooten W, Florence E, Dreezen C, Van Esbroeck M, Fransen K, Alonso A, et al. Five-year immunological outcome of highly active antiretroviral treatment in a clinical setting: results from a single HIV treatment centre. International journal of STD & AIDS 2004. Vol. 15: 523-8.

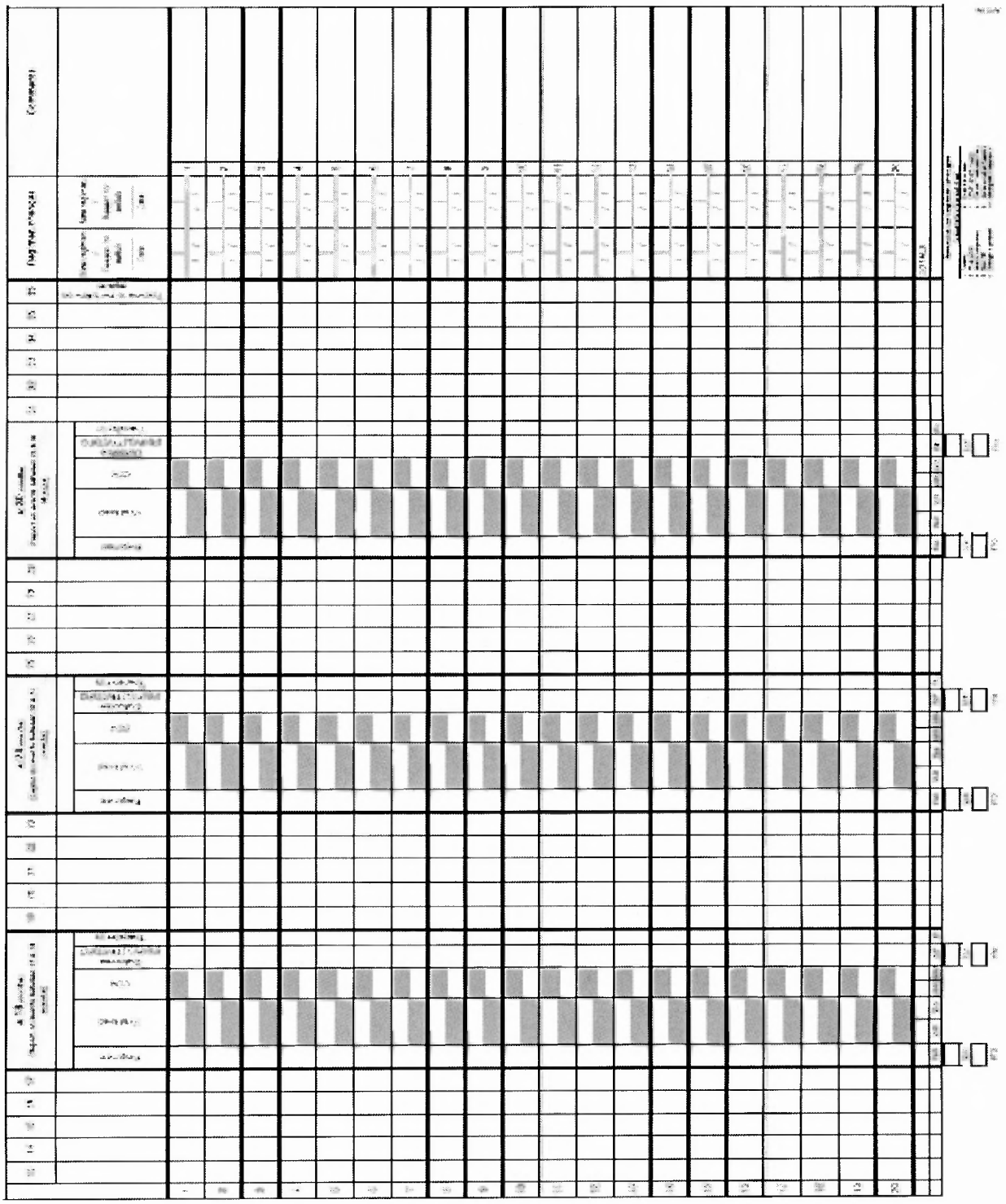
[16] Sterne JA, Hernan MA, Ledergerber B, Tilling K, Weber R, Sendi P, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. Lancet 2005. Vol. 366: 378-84.

[17] Laurent C, Kouanfack C, Koulla-Shiro S, Nkoue N, Bourgeois A, Calmy A, et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. Lancet 2004. Vol. 364: 29-34.

[18] Coetzee D, Hildebrand K, Boulle A, Maartens G, Louis F, Labatala V, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. AIDS (London, England) 2004. Vol. 18: 887-95.
[19] Bekker LG, Myer L, Orrell C, Lawn S, Wood R. Rapid scale-up of a community-based HIV treatment service: programme performance over 3 consecutive years in Guguletu, South Africa. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 2006. Vol. 96: 315-20.
[20] Wools-Kaloustian K, Diero L, Siika A, Sidle J, Tannoutsos CT, Musick B, Einterz R, Fife KH, Tierney WM. Viability and effectiveness of large scale HIV treatment initiatives in Sub Saharan Africa; experience from western Kenya. AIDS (London, England) 2006. Vol. 20: 41-8.
[21] Weidle PJ, Malamba S, Mwebaze R, Sozi C, Rukundo G, Downing R, et al. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. Lancet 2002. Vol. 360: 34-40.
[22] Braitstein P, Brinkhof MW, Dabis F, Schechter M, Boulle A, Miotti P, et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. Lancet 2006. Vol. 367: 817-24.
[23] Doerholt K, Tookey P, Butler K, Lyall H, Sharland M, Novelli V, Riordan A, Dunn D, Walker AS, Gibb DM; Collaborative HIV Paediatric Study. Outcomes for human immunodeficiency virus-1-infected infants in the United Kingdom and Republic of Ireland in the era of effective antiretroviral therapy. Pediatr Infect Dis J 2006. Vol. 25: 420-426.
[24] Matida L, Succi RCD, Marques HHD, Negra MD, Grangeiro A, Hearst N. Improving survival among Brazilian children with perinatally-acquired AIDS. . The Brazilian Journal of Infectious Diseases 2004. Vol 8: 419-423.
[25] Fassinou P, Rouet F, Laguide R, Kouakoussui KA, Timite M, Blanche S, Msellati P. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Côte d'Ivoire. AIDS (London, England) 2004. Vol 18: 1905-13.
[26] Eley B, Davies MA, Apolles P, Cowburn C, Buys H, Zampoli M, et al. Antiretroviral treatment for children. South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde 2006. Vol. 96: 988-93.
[27] Puthanakit T, Akarathum N, Kanjanavanit S, Wannarit P, Sirisanthana T, Sirisanthana V. Efficacy of highly active antiretroviral therapy in HIV-infected children, participating in Thailand's National Access to Antiretroviral program. Clin Infect Dis 2005 Vol 41: 100-107.
[28] World Health Organization. Patient Monitoring Guidelines for HIV Care and Antiretroviral Therapy (ART). Geneva, World Health Organization 2006.
[29] Deschamps AE, van Wijngaerden E, De Saar V, Vandamme AM, van Vaerenbergh K, Ceunen H, Bobbaers H, Peetermans WE, de Vleeschouwer PJ, de Geest S. Prevalence and correlates of non-adherence to antiretroviral therapy in a population of HIV patients using Medication Event Monitoring System. AIDS Patient Care STDS 2004. Vol. 18: 644-57.
[30] Laurent C, Diakhate N, Gueye NF, Toure MA, Sow PS, Faye MA, et al. The Senegalese government's highly active antiretroviral therapy initiative: an 18-month follow-up study. AIDS (London, England) 2002. Vol. 16: 1363-70.

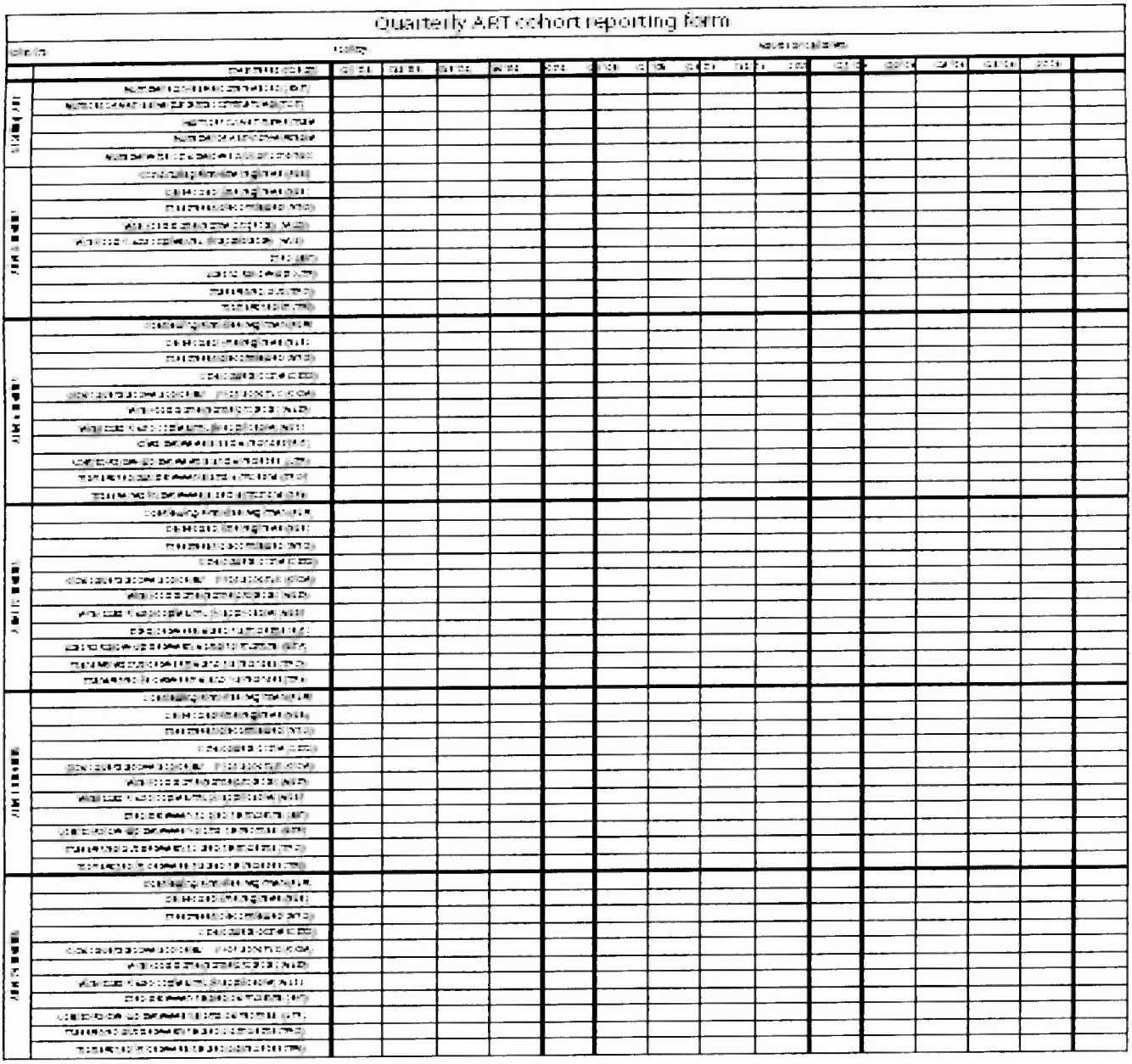
[31] Laurent C, Ndour CT, Gueye PM, Diouf M, Diakhate N, Toure Kane NC, Laniece I, Ndir A, Vergne L, Ndoye I, Mboup S, Sow PS, Delaporte E; ANRS 1215/1290 Study Group. Long term effects of highly active antiretroviral therapy in Senagalese HIV 1 infected adults. Journal of Acq Imm Def. Vol. 38:14-7.
[32] Phillips A, Lampe F, Johnson M, Sabin C. . When should antiretroviral therapy be started for HIV infection? Interpreting the evidence from observational studies. AIDS (London, England) 2003. Vol. 17: 1863-9.
[33] Shisana O, Simbayi LC, Parker W, Zuma K, Bhana A, Connolly C, Jooste S, Pillay V et al. South African National HIV Prevalence, Incidence, Behaviour and Communication Survey. Cape Town, Human Sciences Research Council 2005.

Appendix A: The ART register



Appendix B: The quarterly report form

Western Cape quarterly treatment cohort report



Appendix C: Structured clinical records

Western Cape patient encounter form

Appendix D: The patient held card

Next Visit	D	N	C	B	M	S	Next Visit	D	N	C	B	M	S

D – Doctor, N – Nurse, C – Counsellor, B – Bloods, M – Medication, S – Sputum

PATIENT TREATMENT CARD

Clinic.......................... Clinic Tel. No. ....

Surname..

Full name(s)..

Folder number.......................... DOB: ....

UNIQUE ID

Previous treatment site(s) and folder numbers if transferred

Hospital folder numbers

Previous antiretroviral treatment before start date

Treatment start date d d / m m / y y

Treatment assistant name..

Treatment assistant or carer contact details...........................

Allergies and notes

Date	CD4	HIV RNA	Regimen changes or other interventions, TB treatment, prophylaxis changes, other significant clinical events