Published in final edited form as:
AIDS. 2010 September 10; 24(14): 2263–2270. doi:10.1097/QAD.0b013e32833d45c5.

Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa, 2002–2007

Morna Cornell[1,2], **Anna Grimsrud**[1], **Lara Fairall**[3,4], **Matthew P. Fox**[5,6], **Gilles van Cutsem**[7,1], **Janet Giddy**[8], **Robin Wood**[9], **Hans Prozesky**[10], **Lerato Mohapi**[2], **Claire Graber**[11], **Matthias Egger**[11,12], **Andrew Boulle**[1], and **Landon Myer**[1,13] **for the International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration**

[1]Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, University of Cape Town, Cape Town, South Africa [2]Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa [3]Knowledge Translation Unit, University of Cape Town Lung Institute, University of Cape Town, Cape Town, South Africa [4]Department of Medicine, University of Cape Town, Cape Town, South Africa [5]Center for Global Health & Development, Boston University, Boston, USA [6]Health Economics & Epidemiology Research Office, University of the Witwatersrand, Johannesburg, South Africa [7]Medecins Sans Frontieres, Cape Town, South Africa [8]McCord Hospital, Durban, South Africa [9]The Desmond Tutu HIV Centre, Institute for Infectious Disease & Molecular Medicine, University of Cape Town, South Africa [10]Division of Infectious Diseases, Department of Medicine, University of Stellenbosch, Cape Town, South Africa [11]Division of International and Environmental Health, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland [12]Department of Social Medicine, University of Bristol, Bristol, United Kingdom [13]International Center for AIDS

Corresponding author: Morna Cornell, morna@global.co.za, School of Public Health & Family Medicine, Centre for Infectious Disease Epidemiology & Research, University of Cape Town, Falmouth Building, Anzio Road, Observatory 7925 South Africa, Ph: +27 21 406 6487, Fax: +27 21 406 6764.

Conflict of interest

The authors declare that they have no conflict of interest.

IeDEA Southern Africa Steering Group

Member Sites/cohorts: Anna Coutsoudis, PMTCT Plus, Durban, South Africa; Diana Dickinson, Gaborone Independent Hospital, Gaborone, Botswana; Brian Eley, Red Cross Children's Hospital, Cape Town, South Africa; Lara Fairall, Free State provincial ARV roll-out, South Africa; Tendani Gaolathe, Princess Marina Hospital, Gaborone, Botswana; Janet Giddy, McCord Hospital, Durban, South Africa; Timothy Meade, CorpMed Clinic, Lusaka, Zambia; Patrick MacPhail, Themba Lethu Clinic, Helen Joseph Hospital, Johannesburg, South Africa; Lerato Mohapi, Perinatal HIV Research Unit, Johannesburg, South Africa; Margaret Pascoe, Newlands Clinic, Harare, Zimbabwe; Hans Prozesky, Tygerberg Academic Hospital, Stellenbosch, South Africa; Harry Moultrie, University of Witwatersrand Paediatric HIV Clinics (Harriet Shezi Clinic, Chris Hani Baragwanath Hospital), Johannesburg, South Africa; Karl Technau, University of Witwatersrand Paediatric HIV Clinics (Empilweni Clinic, Rahima Moosa Mother and Child Hospital, Johannesburg, South Africa; Gilles van Cutsem, Khayelitsha ART Programme and Médecins sans Frontières, Cape Town, South Africa; Paula Vaz, Paediatric Day Hospital, Maputo, Mozambique; Ralf Weigel, Lighthouse Clinic, Lilongwe, Malawi; Robin Wood, Gugulethu and Masiphumelele ART Programmes, Cape Town, South Africa.

Central Team: Martin Brinkhof, Matthias Egger, Beatrice Fatzer, Claire Graber and Olivia Keiser, Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland; Andrew Boulle, Morna Cornell, Mary-Ann Davies, Nicola Maxwell, Landon Myer and Anna Grimsrud, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa.

Care and Treatment Programs, and Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA

BACKGROUND

South Africa has the largest ART programme in the world [1]. Between 2004 (the start of the national ART programme) and 2007, an estimated 370,000 people initiated treatment in the public sector [2]. But despite the scope and rapid growth of this programme there are no data on programme outcomes at a national level. The International Epidemiologic Databases to Evaluate AIDS collaboration of Southern Africa (IeDEA-SA) has assembled a series of HIV treatment cohorts from across the country that include approximately 10% of all adults who initiated public sector ART in South Africa by the end of 2007. The aim of this paper is to describe trends in mortality, loss to follow-up (LTFU) and programme retention of these adult patients over the first 5 years of the country's national ART programme.

METHODS

Study design, population & eligibility criteria

The South African cohorts of IeDEA-SA have been described in detail elsewhere [3]. Briefly, the collaboration includes 8 adult cohorts providing ambulatory ART services located in the 4 largest provinces in the country (Western Cape, Free State, Gauteng and Kwazulu-Natal). This analysis included all HIV-positive adults (≥16 years) who initiated ART in these cohorts between 2002 and 2007.

Variables and definitions

Baseline characteristics included demographics (age, sex), available measures of disease severity (CD4 count, WHO stage and viral load) and calendar year of ART initiation. Outcome measures were mortality, LTFU and programme retention. Deaths and transfers were defined by active or passive follow-up at site level. Patients were defined as LTFU if their last patient contact was more than 6 months before the date of closure of the cohort database and were censored at their last contact date. Patients who were transferred out were censored at the transfer date. For patients who started ART but had no further contact with the clinic, one day of follow-up was added to allow their inclusion in survival analyses. Programme retention was defined as those who were enrolled and alive (including transfers out) at analysis closure.

Person-time in the database included patients commencing ART from January 2002 until December 2007. Database closure was on or before 31 December 2008 (with minor variation across cohorts).

Analysis

Baseline characteristics were described with summary statistics (medians, interquartile ranges and proportions). Due to variability in the completeness of baseline data, patient numbers are reported for each analysis. Mean age, median CD4 count and proportion in WHO Stage IV were calculated by year of enrolment. Temporal trends were tested with the nonparametric test for trend across continuous variables (age and CD4). Differences between proportions were tested with the chisquare test. Time to death, LTFU and overall programme retention were analysed using Kaplan-Meier methods and presented by year of enrolment with use of the log rank test for trend of the survivor function.

Separate proportional hazards regression models, stratified by cohort, were used to assess crude and adjusted associations between patient characteristics and different outcomes. We modelled the proportional hazards of death separately for different time periods as the risk factors for death vary, particularly during the first year on ART [4,5]. The proportional hazards assumption was confirmed using Schoenfeld and scaled Schoenfeld residuals. Models were built by adding relevant variables with progressively less complete data, to preserve as many observations as possible. Data on WHO staging, an important predictive variable, were missing for 74% of patients. Consequently, we present 2 final models (including and excluding WHO stage) for each time period. We report findings from the models excluding WHO stage, and where WHO staging impacted appreciably on results, we report this.

Although the national ART roll-out programme started on 1 April 2004, we included a small proportion of adults who had received ART through donor-funded programmes prior to this date. There were no differences in baseline characteristics between patients started in 2002/2003 and those started in 2004, and in a sensitivity analysis (not shown) no aspect of the study findings was substantively different when patients starting ART in 2002/2003 were excluded.

Data were analysed using STATA 11.0 (STATA Corporation, College Station, Texas, USA). Two-sided statistical tests were used at alpha=0.05. All IeDEA-SA sites obtained ethical approval from relevant local institutions before contributing anonymised patient data to this collaborative analysis.

RESULTS

Patient characteristics

This analysis included 44,177 adults who started ART between 2002 and end 2007 (median age 35 years; 68% female, Table 1), contributing a total of 66,434 person-years of follow-up (median 1.27 years, interquartile range (IQR) 0.64–2.20). Among those with CD4 counts at baseline (83%, n=36,549), median CD4 was 103 cells/μL (IQR 45–164), and 27% had a CD4 count <50 cells/μL. The median baseline log viral load measures (available on 18,684 participants, 42%), was 4.9 copies/ml (IQR 4.4–5.4). A total of 11,393 (26%) patients had baseline staging, and 80% of these (n=9,079) were classified WHO stage III/IV.

Temporal changes in patient characteristics and outcomes

Enrolment increased each calendar year, from 1,173 in 2002/03 to 14,728 in 2007 (Table 2). The majority of patients were enrolled in the last 2 years of the period under analysis (63%, n=27,833). With each successive year of the programme, patients were enrolled at older ages and with less advanced HIV disease. Mean age increased from 34 years in 2002/03 to 37 years in 2007 ($p<0.001$). Median CD4 cell count increased from 68 cells/μL in 2002/03 to 113 in 2007 ($p<0.001$). Over the same period, among patients with baseline WHO staging, the proportion of patients with Stage IV disease decreased from 50% to 28% ($p<0.001$).

Between 2002/3 and 2006, 12-month reported mortality declined from 9% to 6% ($p<0.001$) (Table 2, Figure 1a). Meanwhile 12-month LTFU increased with each calendar year of enrolment, from 1% in 2002/03 to 13% in 2006 ($p<0.001$), and 12-month programme retention declined from 90% to 82% over the same period ($p<0.001$) (Table 2). The crude effect of calendar year persisted over 5 years of follow-up (Figures 1a–c).

LTFU increased with duration on treatment (Table 3, Figure 1b) and made an increasing contribution to overall patient attrition. At 6 months on ART, one-third of the losses to

programme were due to mortality: 5% of patients had died while 9% were LTFU. By 36 months, mortality accounted for one-quarter of patient losses: 10% were dead and 30% were LTFU. Overall programme retention dropped from 86% at 6 months to 71% at 24 months and 64% at 36 months.

Associations with baseline characteristics

In all time periods, there was a slight increase in the crude and adjusted risk of death for older patients (adjusted HR 1.03, 95% CI, 1.02–1.04, Table 4a, 12–36 months). There was a strong association between year of enrolment and the risk of death on ART. With each successive year of enrolment the risk of mortality decreased. The risk of death in the first 4 months on ART among those enrolled in 2007 was 31% lower than in those enrolled in 2002/2003 (adjusted HR 0.69, 95% CI 0.52–0.91). Similar results were found in the later durations on treatment.

CD4 count was strongly associated with early mortality on ART in both crude and adjusted analyses: in the first four months on ART, patients with CD4 <0 cells/μL had a 6-fold higher risk of mortality than those with CD4 ≥200 cells/μL (adjusted HR 5.85, 95% CI 4.47–7.65, Table 4a). With longer duration on ART, patients with baseline CD4 count <50 cells/μL continued to be at an elevated risk of death compared with those above 200 cells/μL: the risk was nearly 3-fold higher for patients 4–12 months on treatment (adjusted HR 2.83, 95% CI 2.08–3.85) and 2-fold higher for patients 12–36 months on ART (adjusted HR 1.84, 95% CI 1.24–2.71). The addition of WHO staging attenuated the association between CD4 count and death over all durations on ART, particularly in the group of patients with CD4 count 50–199 cells/μL at baseline.

In univariate and multivariate analysis, younger patients were more likely to be LTFU than older (adjusted HR, 0.99, 95% CI 0.98–0.99, Table 4b). Year of enrolment strongly predicted the risk of LTFU in the early and later time periods on ART: the risk of LTFU increased substantially with each successive year of enrolment and the strength of the association persisted after controlling for baseline age and CD4 count. After adjustment for these factors, patients enrolled on ART in 2007 had a 12-fold increase in the risk of being LTFU during the first year on ART compared with those starting treatment in 2002/03 (adjusted HR 11.89, 95% CI 6.36–22.25). Those with a baseline CD4 count 50–199 cells/μL were less likely to be LTFU in the first year on treatment than those with a CD4 count ≥200 (adjusted HR 0.83, 95% CI 0.76–0.91). This association did not persist when WHO staging was added to the model (adjusted HR 1.03, 95% CI 0.77–1.38).

DISCUSSION

This analysis demonstrates the increasing role played by LTFU over time in the programme outcomes of the South African national ART programme. The rapid pace of ART scale-up in South Africa is evident from the 12-fold increase in this analysis in the number of patients starting ART since 2002, with 63% of all patients initiating ART during 2006 and 2007 alone. While recorded mortality has declined during this period, observed LTFU has increased substantially and presents a major threat to evaluating the effectiveness of the national programme.

Patient retention is a vital measure of the effectiveness of ART services [6,7]. Retention in long-term care is complex, especially in low- and middle-income countries [8–10], but not a new issue: primary health care services have long faced the problem of patient attrition in providing care for chronic diseases [6,11]. A systematic review of ART programmes in Sub-Saharan Africa found large variation in patient retention across programmes, ranging from 46–85% after 2 years on ART [12]. At the start of the South African national programme,

based on experience with other chronic diseases, it was suggested that the ART service may retain 60–80% of patients annually [11]. Retention in the earlier years of the programme exceeded this expectation: at 2 years, 71% of all patients were still known to be in care, but the steady increase in attrition during the first 12 months on ART in successive years of enrolment is cause for concern.

Mortality is one reason for patient attrition: in this cohort, observed mortality at 12 months was 6.6%, which is comparable with results from other developing countries [13]. With successive years of enrolment, 12-month mortality decreased. This may be a true decline due to improved coverage of services and patients enrolling with less advanced HIV disease [14]. It is also plausible that as a programme expands, its ability to accurately ascertain patient deaths deteriorates, and high observed LTFU may be associated with poor mortality ascertainment [15]. It is likely that our study, based on routine surveillance, underestimates true mortality in these cohorts. Recent corrected mortality estimates for single South African ART cohorts (based on linkage to the national death register) found that at 3 years on ART, corrected cumulative mortality was 12–15% [16,17] compared with our uncorrected estimate of 10%. There is an urgent need to improve ascertainment of deaths in low- and middle-income countries [18–20].

Yet even with such underestimation, mortality is not the major reason for patient attrition in large ART programmes in developing countries. The greater threat to the success of the South African ART programme may be the observation of high levels of LTFU, insofar as this outcome reflects patients who have truly left care. The size and pace of ART scale-up may have contributed to observed LTFU. The programme has grown in size dramatically, with our combined cohort increasing enrolment 12-fold over 5 years. Such rapid increases have placed considerable strain on health services that were already overburdened [8,16,21] and may have undermined the programme's ability to monitor and retain patients in care. During 2007 alone, 33% of patients in this study were enrolled onto ART: compared with the 2002/2003 cohort of patients, they had a 12-fold higher risk of appearing LTFU. In addition, with longer duration on ART, observed LTFU accounted for an increasing proportion of overall programme attrition: from 9% at 6 months to 29% at 36 months on ART.

If the rapid expansion of ART services does increase observed LTFU, the situation may worsen as countries continue to expand access to HIV treatment. Based on 2002 WHO treatment guidelines, adult ART coverage in South Africa was an estimated 40% in 2008 [22]. In addition, the South African government recently revised its treatment guidelines to include all infected infants <1 year of age, pregnant women with CD4 counts ≤350 cells/μL, patients co-infected with TB [23]. South Africa and many other countries in sub-Saharan Africa will need to continue to expand services while retaining large numbers of patients in care. This will require strengthening systems for chronic disease care in these countries[6], where most health programmes are oriented towards episodic illnesses and acute care.

Successfully re-orienting health systems towards long-term chronic care will require a better understanding of the phenomenon of LTFU. Often viewed as a single construct, observed LTFU in an ART cohort more likely represents a range of patient outcomes including patients truly LTFU (ie. lost to care) as well as those classified LTFU through administrative error or inadequate patient monitoring systems [15,24]. In a situation of rapid scale-up of ART in resource-limited health systems, the ability to capture and report patient data may become increasingly inadequate [24]. Indeed, our results suggest that larger cohorts may have become more subject to these challenges in recent years. For example, the apparently sharp increase in observed LTFU among patients enrolled in 2007 is likely to reflect the cumulative burden of increasing patient numbers on both ART services and health

informatics systems. This phenomenon may be particularly acute at larger and rapidly expanding ART sites, some of which enrolled up to 50% of their cumulative number of patients in 2007 alone.

Despite the scope of the problem of observed LTFU in ART services in southern Africa, relatively little is known about this phenomenon. These cohorts, which are largely funded by the national Department of Health, report active tracing (ie dedicated resources to undertake one or more of the following: telephone call, home follow-up, physician's report and/or data linkage [3]. However, largely due to resource constraints, funding for patient follow-up, particularly at this scale, is limited. There is a small literature on factors associated with patient retention highlighting the possible role of patient preparation [25], treatment supporters [26], patient costs [10,27], improved databases [24], community support [28] and simplified services [6]. However, research is needed to better understand observed LTFU and the relative contributions of true LTFU (patients dropping out of ART services) versus administrative LTFU (patients who are retained in care but appear LTFU due to problems with data capturing and reporting). In contrast to these individuals, patients who are truly LTFU are likely to be non-adherent to treatment and at higher risk of death [16,29]. In addition, they face increased risk of drug resistance to ART, undermining the long-term effectiveness of treatment programmes [12,16]. Additional research is needed into the programme-level determinants of LTFU, better characterization of patients classified LTFU and insights into patients' movements in and out of care.

This is the first report on outcomes from multiple cohorts in the world's largest antiretroviral therapy programme, and to our knowledge, the largest analysis of individuals starting ART in sub-Saharan Africa. It is strengthened by up to 5 years of patient follow-up on more than 40,000 patients. The results are likely generalisable to the patient population accessing public sector ART in most of South Africa [3] where 80% of the population rely on the public sector for services [30]. However, this analysis has several important limitations. As is the case with other large-scale ART programmes based on routine monitoring and evaluation, it is constrained by issues of outcome ascertainment and missing data [24]. Outcome ascertainment should improve as more cohorts in South Africa link to the death register, presumably increasing observed mortality and decreasing observed LTFU. Data completeness may continue to present a challenge, particularly as programmes continue to expand. WHO staging were the least complete data point in this analysis, yet their inclusion in multivariate analysis impacted on the association between baseline CD4 count and outcomes, highlighting the importance of complete baseline data. Finally, this paper reports on averages across cohorts which may differ in data quality, completeness and outcome ascertainment. Despite these constraints, this analysis utilizes routinely collected data to provide valuable insight into the effectiveness of a huge national programme, and has important implications for South Africa and for other programmes in similar contexts.

In summary, this analysis demonstrates that the South African national ART programme has undergone rapid scale-up over the past 5 years. While recorded mortality has decreased, programme retention has deteriorated, as decreasing patient mortality has been greatly offset by high and increasing levels of LTFU. This increased LTFU may represent true loss to care, but also may be due to increasing difficulty in monitoring patients enrolling into care as well as patient movements in and out of care. These possibilities require further investigation. Innovative, effective strategies are needed to follow and retain patients in large HIV treatment programmes while rapidly expanding access to ART services.

Acknowledgments

LF, MF, GvC, JG, RW, HP & LM established/maintained cohorts and provided data. MC was responsible for writing the paper. AG undertook statistical analyses. MC, LM, AB & AG interpreted the data. All authors commented on the draft manuscripts and approved the final version.

We thank all the patients who contributed data to this analysis, and the staff who provide their care. Thanks to all staff at participating sites for collection and preparation of data contributed to IeDEA-Southern Africa. Thanks to Nathan Ford, Patrick MacPhail and Max Bachmann for comments on the manuscript, and to Nicola Maxwell and Venessa Timmerman for preparing the data for analysis. We acknowledge all those who died without access to ART.

Funding

Support for this study was provided by the US National Institute of Allergy and Infectious Diseases (NIAID) through the International epidemiological Databases to Evaluate AIDS, Southern Africa (IeDEA-SA), Grant no 5U01AI069924-04.

REFERENCES

1. World Health Organization, UNAIDS, UNICEF. Towards Universal Access: Scaling up Priority HIV/AIDS Interventions in the Health Sector: Progress Report. Geneva: WHO; 2007.
2. Department of Health. Progress Report on Declaration of Commitment on HIV and AIDS: Republic of South Africa: Reporting Period: January 2006 – December 2007. 2008.
3. Cornell, M.; Technau, K.; Fairall, LR.; Wood, R.; Moultrie, H.; Van Cutsem, G., et al. Monitoring the South African National Antiretroviral Treatment Programme, 2003 – 2007: The IeDEA Southern Africa Collaboration; South African Medical Journal. 2009. p. 653-660.Full text available at: http://www.samj.org.za/index.php/samj/article/viewFile/3437/2485
4. Lawn SD, Harries AD, Anglaret X, Myer L, Wood R. Early mortality among adults accessing antiretroviral treatment programmes in sub-Saharan Africa. Aids. 2008; 22:1897–1908. [PubMed: 18784453]
5. Zachariah R, Harries K, Moses M, Manzi M, Line A, Mwagomba B, Harries AD. Very early mortality in patients starting antiretroviral treatment aqt primary health centres in rural Malawi. Trop Med Int Health. 2009; 14:713–721. [PubMed: 19497082]
6. Harries AD, Zachariah R, Jahn A, Schouten EJ, Kamoto K. Scaling up antiretroviral therapy in Malawi-implications for managing other chronic diseases in resource-limited countries. J Acquir Immune Defic Syndr. 2009; 52 Suppl 1:S14–S16. [PubMed: 19858929]
7. Massaquoi M, Zachariah R, Manzi M, Pasulani O, Misindi D, Mwagomba B, et al. Patient retention and attrition on antiretroviral treatment at district level in rural Malawi. Trans R Soc Trop Med Hyg. 2009; 103:594–600. [PubMed: 19298993]
8. Boulle A, Ford N. Scaling up antiretroviral therapy in developing countries: what are the benefits and challenges? Sex Transm Infect. 2007; 83:503–505. [PubMed: 18024708]
9. Harries AD, Schouten EJ, Libamba E. Scaling up antiretroviral treatment in resource-poor settings. Lancet. 2006; 367:1870–1872. [PubMed: 16753490]
10. Losina E, Toure H, Uhler LM, Anglaret X, Paltiel AD, Balestre E, et al. Cost-effectiveness of preventing loss to follow-up in HIV treatment programs: a Cote d'Ivoire appraisal. PLoS Med. 2009; 6 e1000173.
11. Myer L, el-Sadr W. Expanding access to antiretroviral therapy through the public sector--the challenge of retaining patients in long-term primary care. S Afr Med J. 2004; 94:273–274. [PubMed: 15150939]
12. Rosen S, Fox MP, Gill CJ. Patient retention in antiretroviral therapy programs in sub-saharan Africa: a systematic review. PLoS Med. 2007; 4:e298. [PubMed: 17941716]
13. 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; 367:817–824. [PubMed: 16530575]

14. Boulle A, Bock P, Osler M, Cohen K, Channing L, Hilderbrand K, et al. Antiretroviral therapy and early mortality in South Africa. Bull World Health Organ. 2008; 86:678–687. [PubMed: 18797643]
15. Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. PLoS One. 2009; 4:e5790. [PubMed: 19495419]
16. Boulle A, Van Cutsem G, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. Aids. 2010:24.
17. Fox MP, Brennan A, Maskew M, PacPhail P. Using vital registration data to update mortality among patients lost to follow-up from ART programmes: evidence from the Themba Lethu Clinic, South Africa. Trop Med Int Health. 2010 In Press.
18. Mathers C, Boerma T. Mortality Measurement Matters: Improving Data Collection and Estimation Methods for Child and Adult Mortality. PLoS Med. 2010:7.
19. Murray CJL, Rajaratnam JK, Marcus J, Laakso T, AD L. What Can We Conclude from Death Registration? Improved Methods for Evaluating Completeness. PLoS Med. 2010:7.
20. Obermeyer Z, Rajaratnam JK, Park CH, Gakidou E, Hogan MC, et al. Measuring Adult Mortality Using Sibling Survival: A New Analytical Method and New Results for 44 Countries, 1974–2006. PLoS Med. 2010:7.
21. Coovadia H, Jewkes R, Barron P, Sanders D, McIntyre D. The health and health system of South Africa: historical roots of current public health challenges. The Lancet. 2009:11–28.
22. Adam MA, Johnson L. Estimation of adult antiretroviral treatment coverage in South Africa. South African Medical Journal. 2009; 99:661–667. [PubMed: 20073293]
23. Department of Health. The South African Antiretroviral Treatment Guidelines 2010; 2010. p. 13Full text available at http://www.sanac.org.za/documents/2010%20ART%20Guideline-Short.pdf
24. Forster M, Bailey C, Brinkhof MW, Graber C, Boulle A, Spohr M, et al. Electronic medical record systems, data quality and loss to follow-up: survey of antiretroviral therapy programmes in resource-limited settings. Bull World Health Organ. 2008; 86:939–947. [PubMed: 19142294]
25. Coetzee D, Boulle A, Hildebrand K, Asselman V, Van Cutsem G, Goemaere E. Promoting adherence to antiretroviral therapy: the experience from a primary care setting in Khayelitsha, South Africa. Aids. 2004; 18 Suppl 3:S27–S31. [PubMed: 15322481]
26. Nachega JB, Knowlton AR, Deluca A, Schoeman JH, Watkinson L, Efron A, et al. Treatment supporter to improve adherence to antiretroviral therapy in HIV-infected South African adults. A qualitative study. J Acquir Immune Defic Syndr. 2006; 43 Suppl 1:S127–S133. [PubMed: 17133196]
27. Maskew M, MacPhail P, Menezes C, Rubel D. Lost to follow up: contributing factors and challenges in South African patients on antiretroviral therapy. S Afr Med J. 2007; 97:853–857. [PubMed: 17985056]
28. Zachariah R, Teck R, Buhendwa L, Fitzerland M, Labana S, Chinji C, et al. Community support is associated with better antiretroviral treatment outcomes in a resource-limited rural district in Malawi. Trans R Soc Trop Med Hyg. 2007; 101:79–84. [PubMed: 16962622]
29. Yu JK, Chen SC, Wang KY, Chang CS, Makombe SD, Schouten EJ, Harries AD. True outcomes for patients on antiretroviral therapy who are "lost to follow-up" in Malawi. Bull World Health Organ. 2007; 85:550–554. [PubMed: 17768504]
30. Barron, P.; Roma-Reardon, J., editors. Health Systems Trust. 2008. South African Health Review 2008.

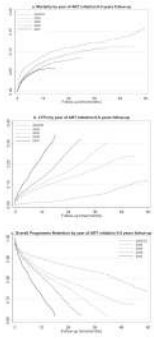

Figure 1.
Kaplan-Meier plots showing by year of ART initiation: (a) 60-month mortality, (b) 60-month loss-to-follow-up, (c) 60-month programme retention

Table 1

Patient characteristics at ART initiation

Characteristic	Adults (≥16 yrs) n=44,177
Sex, *n(%)*	**44,177 (100)**
Female, *n (%)*	29,904 (67.7)
Age, *n(%)*	**44,177 (100)**
Adults (years), *median (IQR)*	35.0 (29.9–41.6)
Age categories, *n(%)*	
16–24	2,306 (5.2)
25–34	17,654 (40.0)
35–44	16,177 (36.6)
45+	8,040 (18.2)
Year of initiation, *n(%)*	**44,177 (100)**
2002 & 2003	1,173 (2.7)
2004	5,262 (11.9)
2005	9,909 (22.4)
2006	13,105 (29.7)
2007	14,728 (33.3)
Absolute CD4 cell count (cell/μL), *n(%)*	**36,549 (82.7)**
All adults, *median (IQR)*	103 (45–164)
CD4 cell count, categorical, *n(%)*	
<50	9,947 (27.2)
50–199	22,703 (62.1)
>=200	3,899 (10.7)
HIV RNA level, log_{10} copies/ml, *n(%)*	**18,684 (42.3)**
Median (IQR)	4.9 (4.4–5.4)
RNA level, categorical, n(%)	
<=5 Log	10,405 (55.7)
>5 Log	8,279 (44.3)
WHO stage, *n(%)*	**11,393 (25.8)**
I	979 (8.6)
II	1,335 (11.7)
III	5,463 (48.0)
IV	3,616 (31.7)

Table 2

Baseline characteristics and 12-month outcomes by calendar year of ART initiation

	YEAR OF ENROLMENT				
	2002/03	**2004**	**2005**	**2006**	**2007**
Age	34.3	35.7	35.7	36.2	36.9
mean (95%CI)	(33.9–34.8)	(35.4–35.9)	(35.6–35.9)	(36.0–36.3)	(36.8–37.1)
CD4	68	87	102	106	113
med (IQR)	(23–130)	(38–147)	(44–160)	(46–168)	(51–170)
(n=36,549)					
Patients in Stage IV, *n(%)*	434	708	998	998	478
(n=11,393)	(50.2)	(38.5)	(31.3)	(26.5)	(27.7)
12-month mortality	8.9	7.2	7.4	6.2	5.6
% (95% CI)	(7.4–10.7)	(6.5–7.9)	(6.9–7.9)	(5.8–6.7)	(5.1–6.0)
12-month LTFU	1.1	8.6	10.3	13.1	23.5
% (95% CI)	(0.6–1.9)	(7.9–9.4)	(9.7–10.9)	(12.5–13.7)	(22.7–24.3)
12-month retention	90.1	84.8	83.1	81.5	72.3
% (95% CI)	(88.2–91.7)	(83.8–85.8)	(82.3–83.8)	(80.8–82.1)	(71.4–73.1)

Table 3

Kaplan-Meier estimates of mortality, loss-to-follow-up and overall programme retention by duration of follow-up (n=44,177 at baseline)

Duration of follow-up	n(%)	Mortality *% (95% CI)*	Loss-to-follow-up *% (95% CI)*	Overall retention *% (95% CI)*
6 months	35,627 (80.6)	4.8 (4.6–5.0)	9.3 (9.0–9.6)	86.4 (86.1–86.7)
12 months	26,315 (59.6)	6.6 (6.3–6.8)	14.4 (14.1–14.8)	80.0 (79.6–80.3)
18 months	18,788 (42.5)	7.6 (7.4–7.9)	18.8 (18.4–19.3)	75.0 (74.5–75.4)
24 months	13,115 (29.7)	8.5 (8.2–8.8)	22.4 (21.9–22.9)	71.0 (70.5–71.5)
36 months	5,486 (12.4)	9.7 (9.4–10.1)	28.7 (28.0–29.3)	64.4 (63.8–65.0)
48 months	803 (1.8)	10.6 (10.1–11.2)	33.3 (32.4–34.2)	59.6 (58.7–60.5)
60 months	185 (0.4)	12.9 (11.4–14.7)	35.8 (34.3–37.4)	55.9 (54.1–57.6)

Table 4

Table 4a: Cox's proportional hazards models of 0–4 month, 4–12 month and 12–36 month mortality by baseline characteristics and year of ART initiation, stratified by cohort. Multivariate models adjusted for all variables shown (Model 1 excludes WHO staging; Model 2 includes WHO staging)

	0–4 months			4–12 months			12–36 months		
	Univariate	Multivariate Models		Univariate	Multivariate Models		Univariate	Multivariate Models	
		Model 1 (n=36,549)	Model 2 (n=9,951)		Model 1 (n=31,038)	Model 2 (n=8,343)		Model 1 (n=21,992)	Model 2 (n=6,055)
Variables	*HR(95% CI)*	*HR(95% CI)*	*HR(95% CI)*	*HR(95% CI)*	*HR(95% CI)*	*HR(95% CI)*	*HR(95% CI)*	*HR(95% CI)*	*HR(95% CI)*
Age (years)	1.01 (1.00–1.02)	1.01 (1.00–1.01)	1.01 (1.00–1.02)	1.02 (1.01–1.02)	1.02 (1.01–1.03)	1.03 (1.01–1.04)	1.03 (1.02–1.04)	1.03 (1.02–1.04)	1.05 (1.03–1.07)
Year of enrolment									
2002/2003	1	1	1	1	1	1	1	1	1
2004	0.65 (0.50–0.86)	0.62 (0.46–0.82)	0.82 (0.60–1.13)	1.03 (0.70–1.53)	0.89 (0.59–1.35)	0.98 (0.61–1.57)	1.13 (0.78–1.65)	1.03 (0.68–1.57)	1.01 (0.67–1.59)
2005	0.71 (0.55–0.91)	0.73 (0.56–0.96)	0.70 (0.620–0.96)	0.95 (0.65–1.39)	0.87 (0.58–1.30)	0.85 (0.54–1.33)	0.86 (0.60–1.27)	0.82 (0.54–1.25)	0.73 (0.45–1.20)
2006	0.56 (0.43–0.72)	0.62 (0.47–0.81)	0.62 (0.45–0.85)	0.83 (0.57–1.22)	0.73 (0.49–1.10)	0.64 (0.40–1.02)	0.69 (0.45–1.05)	0.66 (0.42–1.06)	0.84 (0.23–1.22)
2007	0.63 (0.49–0.82)	0.69 (0.52–0.91)	0.56 (0.37–0.86)	0.49 (0.32–0.73)	0.47 (0.30–0.72)	1.10 (0.37–3.22)	0.24 (0.11–0.51)	0.25 (0.11–0.57)	-
CD4 (cells/μL)									
≥200	1	1	1	1	1	1	1	1	1
50–199	1.67 (1.27–2.19)	1.64 (1.25–2.16)	0.93 (0.60–1.44)	1.50 (1.11–2.03)	1.41 (1.04–1.91)	0.78 (0.46–1.32)	1.24 (0.85–1.81)	1.16 (0.79–1.69)	1.07 (0.51–2.22)
<50	5.95 (4.55–7.78)	5.85 (4.47–7.65)	2.80 (1.83–4.28)	3.00 (2.21–4.07)	2.83 (2.08–3.85)	1.53 (0.90–2.59)	1.94 (1.31–2.87)	1.84 (1.24–2.71)	1.39 (0.66–2.95)
WHO Stage									
I & II	1	-	1	1	-	1	1	-	1
III	3.27 (2.03–5.28)	-	2.35 (1.41–3.91)	2.01 (1.21–3.34)	-	1.49 (0.87–2.53)	1.48 (0.83–2.66)	-	1.32 (0.72–2.54)
IV	10.21 (6.41–16.26)	-	5.82 (3.51–9.62)	4.12 (2.50–6.79)	-	2.78 (1.62–4.74)	2.54 (1.43–4.52)	-	1.98 (1.04–3.75)
HIV RNA level, log_{10} copies/ml									
<=5 Log	1	-	-	1	-	-	1	-	-
>5 Log	1.90 (1.63–2.22)	-	-	1.32 (1.09–1.59)	-	-	1.42 (1.12–1.82)	-	-

AIDS. Author manuscript; available in PMC 2011 September 10.

Table 4b: Cox's proportional hazards models of LTFU at 0–12 months and 12–36 months by baseline characteristics and year of ART initiation, stratified by cohort. Multivariate models adjusted for all variables shown (Model 1 excludes WHO staging; Model 2 includes WHO staging)

	0–12 months			12–36 months		
	Univariate	Multivariate Models		Univariate	Multivariate Models	
		Model 1 (n=36,549)	Model 2 (n=9,951)		Model 1 (n=21,992)	Model 2 (n=6,055)
Variables	***HR(95% CI)***	***HR(95% CI)***	***HR(95% CI)***	***HR(95% CI)***	***HR(95% CI)***	***HR(95% CI)***
Age (years)	0.99* (0.99–0.99)	0.99** (0.99–0.99)	0.98 (0.97–0.99)	0.99 (0.98–0.99)	0.99 (0.98–0.99)	0.97 (0.96– 0.99)
Year of enrolment						
2002 & 2003	1	1	1	1	1	1
2004	6.69 (3.77–11.89)	5.74 (3.06–10.79)	2.63 (1.29–5.39)	2.76 (1.96–3.89)	3.37 (2.20–5.15)	3.54 (2.17–5.77)
2005	7.68 (4.34–13.59)	6.29 (3.36–11.76)	4.99 (2.54–9.80)	4.13 (2.92–5.84)	4.98 (3.25–7.65)	3.57 (3.94–10.93)
2006	9.40 (5.32–16.61)	7.67 (4.10–14.34)	9.27 (4.76–18.05)	7.27 (5.11–10.35)	8.01 (5.17–12.40)	10.62 (5.73–19.68)
2007	15.34 (8.68–27.13)	11.89 (6.36–22.25)	10.89 (5.47–22.10)	12.77 (8.78–18.59)	12.58 (7.91–20.00)	-
CD4 (cells/μL)						
≥200	1	1	1	1	1	1
50–199	0.77 (0.71–0.85)	0.83 (0.76–0.91)	1.03 (0.77–1.38)	0.92 (0.80–1.07)	0.98 (0.85–1.14)	0.55 (0.39–0.78)
<50	0.97 (0.88–1.07)	1.05 (0.95–1.15)	1.30 (0.95–1.79)	0.85 (0.72–1.00)	0.91 (0.77–1.08)	0.56 (0.38–0.83)
WHO stage						
I & II	1	-	1	1	-	1
III	0.98 (0.79–1.21)	-	1.16 (0.92–1.46)	0.86 (0.65–1.13)	-	1.07 (0.78–1.45)
IV	1.12 (0.90–1.39)	-	1.35 (1.04–1.74)	0.67 (0.49–0.91)	-	0.95 (0.68–1.35
HIV RNA level, $\log_{10}$ copies/ml						
<=5 Log	1	-	-	1	-	-
>5 Log	0.98 (0.89–1.08)	-	-	0.92 (0.81–1.03)	-	-

*0.989 (0.986–0.993)

**0.989 (0.985–0.992)