The effectiveness and determinants of effectiveness of antiretroviral therapy for adults in the Western Cape Province of South Africa

By

Andrew Boulle

Thesis presented for the degree of
Doctor of Philosophy
in the School of Public Health and Family Medicine
University of Cape Town

October 2009

University of Cape Town

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By
Andrew Boulle
MBChB, MSc, FCPHM(SA)

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Supervisors: Professors Jonny Myers and Gary Maartens

This thesis is presented in fulfilment of the requirements for the degree of Doctor of Philosophy (PhD) in the School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town. The work on which this thesis is based is original research and has not, in whole or in part, been submitted for another degree at this or any other university. The contents of this thesis are entirely the work of the candidate, or in the case of multi-authored published papers, constitutes work for which the candidate was the lead author. The contribution of the candidate to included multi-authored papers is further delineated in the preface to the thesis and in the introduction to each included paper as appropriate.

Andrew Boulle
October 2009

Abstract

Antiretroviral therapy (ART) first became available in the public sector in the Western Cape Province in Khayelitsha in 2001. This thesis describes the effectiveness of ART in Khayelitsha and the Province, following adult patients for up to five years on ART, and examining temporal trends over seven years during which time the availability of ART in the Province increased dramatically. Associations are explored with a range of clinical outcomes, and regimen durability and tolerability are described, together with regimen effectiveness when ART is administered to patients co-infected with tuberculosis.

The results chapters of the thesis are presented in the form of published or submitted papers. The first paper corrects for under-ascertainment of mortality through linkages with the death registry. After five years on ART, four out of five patients were still alive. Survival did not deteriorate in more recent years despite the large increase in patient numbers. Patients who remained virologically suppressed experienced on average continued CD4 count recovery throughout follow-up to five years. The second paper describes the tolerability of each commonly used first-line antiretroviral drug in two townships in the Western Cape. Treatment-limiting toxicities were frequent and continued throughout follow-up in patients on stavudine (21% by 3 years on ART). Symptomatic hyperlactataemia or lactic acidosis as well as lipodystrophy were strongly associated with women initiating ART with a high initial body mass. The third paper explores the effectiveness of ART when co-administered with tuberculosis treatment, identifying that co-infected patients initiating nevirapine-based ART may be at a higher risk of virological failure, but that concurrent tuberculosis treatment did not otherwise compromise ART outcomes. The fourth paper, based on a household survey, provides an in-depth description of the Khayelitsha population demonstrating comparability with many of the urban settings in which ART is provided in the region. The final paper demonstrates that outcomes have not been compromised by the wider availability of ART in the Western Cape Province.

The thesis concludes that the Khayelitsha and Provincial analyses provide considerable reassurance that the anticipated benefits of ART have not to date been eroded by health system weaknesses or contextual challenges.

Acknowledgements

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- I thank my supervisors, Jonny Myers and Gary Maartens, for their patience, insights and constant support.
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- For the analysis on regimen substitutions, I thank Catherine Orrell, Landon Myer and Robin Wood for urging us to combine data with the Gugulethu cohort and supporting the analysis.
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Preface

This thesis includes published papers, as per general provision 6.7 in the General Rules for the Degree of Doctor of Philosophy (PhD) of the University of Cape Town, and with the approval in 2008 of the University Doctoral Degrees Board. The following five papers are formally included as part of the thesis:

1. 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, in press.

2. Boulle A, Orrel C, Kaplan R, Van Cutsem G, McNally M, Hilderbrand K, et al. Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort. *Antivir Ther* 2007;12(5):753-60

3. Boulle A, Van Cutsem G, Cohen K, Hilderbrand K, Mathee S, Abrahams M, et al. Outcomes of nevirapine- and efavirenz-based antiretroviral therapy when coadministered with rifampicin-based antitubercular therapy. *JAMA* 2008;300(5):530-9.

4. Boulle A, Hilderbrand K, Menten J, Coetzee D, Ford N, Matthys F, et al. Exploring HIV risk perception and behaviour in the context of antiretroviral treatment: results from a township household survey. *AIDS Care* 2008;20(7):771-81.

5. 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(9):678-87.

The contribution of the candidate is discussed as part of an introduction to each paper (pages 41, 55, 65, 77 & 91). In summary, the candidate was the lead and corresponding author on all of the included papers, and drafted all versions of the manuscripts. All co-authors critically reviewed and approved the submitted manuscripts, and any comments were assessed by and where appropriate integrated

by the candidate. The senior or a senior co-author on each paper has separately confirmed to the University of Cape Town Doctoral Degrees Board that the included papers overwhelmingly reflect the candidate's own scientific work.

The candidate personally conducted all of the analyses in the included papers (as outlined in the methods sections of the papers), with the exception of the household survey, where the analysis was conducted in parallel in Cape Town and Antwerp. In addition, four of the papers report on specific analyses embedded in ongoing HIV cohort studies. The candidate played a key role in the establishment of and ongoing maintenance of these cohort studies over a seven year period, including being involved in primary data collection through the provision of clinical care for some of this time. Further details of the candidate's involvement in the specifics of data collection and management are included as part of the methods section of the introductory chapter (Chapter 1, Section D, page 38).

Abbreviations

3TC	lamivudine
AHR	adjusted hazard ratio
ABC	abacavir
ART	antiretroviral therapy
ART-LINC	Antiretroviral Therapy in Lower Income Countries
AZT	azidothymidine / zidovudine
BMI	body mass index
BPI	boosted protease inhibitors
d4T	stavudine
DAI	Drug Access Initiative
ddI	didanosine
EFV	efavirenz
eKapa	database application used in the Khayelitsha antiretroviral cohort
FDC	fixed-dose combination
GFATM	Global Fund for Aids, Tuberculosis and Malaria
GIS	geographical information system
HIV	Human Immunodeficiency Virus
HLA	human leucocyte antigen
IAS	International AIDS Society
IeDEA	International Epidemiologic Databases to Evaluate Aids
MSF	Médecins Sans Frontières
NGO	non-governmental organisation
NNRTI	non-nucleoside reverse transcriptase inhibitors
NRTI	nucleoside reverse transcriptase inhibitors
NVP	nevirapine
PEPFAR	President's Emergency Plan for AIDS Relief
PI	protease inhibitor
PMTCT	prevention of mother-to-child transmission
REC REF	Research Ethics Committeer reference number (UCT)
SD-NVP	single-dose nevirapine
SHLA	symptomatic hyperlactataemia or lactic acidosis
SMR	standardised mortality ratio
TAMS	thymidine analogue mutations
TDF	tenofovir
UCT	University of Cape Town
UNAIDS	The Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

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Chapter 1: Introduction and literature review

Section A: Introduction

The contribution of Human Immunodeficiency Virus (HIV) to morbidity and mortality in Southern Africa is well described. In South Africa alone, at the conclusion of the period covered by this thesis (2001-2007), the number of deaths estimated to be due to HIV infection exceeded 1,000 a day, the equivalent to the number of deaths from all other causes. Life expectancy at birth in South Africa fell from 63 years in 1990 to 51 years in 2006.[1]

This study was conceived in the early years of the Khayelitsha antiretroviral treatment programme, a project started with the express aim of demonstrating the feasibility of antiretroviral therapy (ART) in this region, at a time when internationally momentum in support of ART provision in poor countries was just starting, and when nationally bitter political contestation surrounded antiretroviral interventions. Over time the project has been assimilated into much larger provincial and national programmes, and at the conclusion of the study, findings are reflective of these larger programmes.

The Western Cape Province, and Khayelitsha more specifically, by virtue of having provided ART for longer, are particularly well-placed to address questions of effectiveness and areas of clinical uncertainty in ART provision in this setting. At the start of this study in 2004, the Khayelitsha ART cohort had just published early findings of outcomes at two years on ART, that would later be widely cited as evidence of ART effectiveness in this setting.[2] Projects funded by the Global Fund for Aids, Tuberculosis and Malaria (GFATM) and the United States bilateral President's Emergency Plan for AIDS Relief (PEPFAR) were in their infancy, and the South African national treatment plan had just been launched. Khayelitsha was therefore one of the few projects with sufficient data in terms of patient numbers, duration of follow-up and data quality, that could address some of the areas of clinical uncertainty, and this was the initial focus of analyses. More recently, as the

number of publishing HIV treatment cohorts in Southern Africa has increased, the focus has shifted to the larger Western Cape provincial programme, to determine programme effectiveness at scale, to find ways of collecting monitoring data from these larger programmes, and to determine the longer term outcomes given increasing loss to follow-up of patients and poorer outcome ascertainment.

Section B: Background and literature review

Pre-existing data on ART efficacy and effectiveness

Azidothymidine (AZT) was originally developed in the 1960's as a candidate drug that would interfere with DNA replication in replicating cancer cells,[3] and was tested for activity against HIV in 1985. AZT inhibits viral replication by synthetically replacing the nucleoside thymidine triphosphate as a substrate for the reverse transcriptase enzyme, hence the class of drugs being termed nucleoside reverse transcriptase inhibitors (NRTI's). The first clinical trial to test AZT in humans with HIV was prematurely halted in 1986 due to the survival benefit observed with an average 4-months of follow-up.[4] Only a single patient out of 145 who received AZT had died compared to 19 in the 137 patients who had received placebo. The same and subsequent studies demonstrated however that the benefit waned with time: the median survival from the onset of AIDS with AZT use was 3 years.[5-6] A number of studies also identified that the survival benefits were confined to patients starting treatment with lower CD4 counts (< 200 cells/μL).[7-9] A meta-analysis of 15 trials later estimated the effect (Peto odds ratio) of therapy with AZT over placebo to be 0.70 for progression to AIDS or death.[10]

Additional antiretrovirals in the same class proved effective, including zalcitibane, didanosine (ddI), lamivudine (3TC), and stavudine (d4T). The first trials to enrol patients onto dual therapy began as early as 1992, and by 1996 there was a strong evidence-base for the superiority of combination therapy over mono-therapy.[11-13] In the Delta trial for example, treatment-naïve adults with AIDS or a CD4 count below 350 cells/μL who received AZT and ddI had mortality reduced by 42% compared to those who received AZT alone.[11] A subsequent meta-analysis of 16 trials estimated the effect size for the progression to AIDS or death to be 0.60 comparing dual to monotherapy.[10]

New classes of antiretroviral, the protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTI's), were developed, enabling the construction of three-drug regimens. The first trial to demonstrate the clinical efficacy of three-drug

ART reported in 1997, in which patients were randomized to receive AZT and 3TC with and without indinavir.[14] Patients with initial CD4 counts below 200 cells/μL receiving the three drug treatment had progression to AIDS or death halved relative to those on two drugs. A subsequent meta-analysis of 9 trials estimated the effect size for the progressions to AIDS or death to be 0.62 comparing triple to dual therapy.[10]

The progression of the standard of care from mono to dual to triple therapy, meant that the efficacy of triple therapy as compared to no therapy would never be tested in a direct clinical trial. Subsequent estimates, based on complex modelling within antiretroviral treatment cohorts, have estimated that triple therapy reduces mortality or progression to AIDS by 86% compared to no treatment, and by 96% in patients starting treatment with CD4 counts below 200 cells/μL.[15]

Effectiveness

Following the evidence from clinical trials as to the efficacy of ART, cohort studies were able to demonstrate that the improvements in survival and reductions in disease progression were also evident in these real world settings. In British Columbia in Canada, patients were 1.9 times more likely to die after adjustment for other predictors of survival during the era when only mono-therapy was available compared to the era when two drugs were available.[16] Patients who received two drugs were in turn 3.2 times more likely to die compared to patients started on ART in the triple-therapy era.[17] This temporal trend was similarly observed in the Swiss HIV Cohort, with a 73% reduction in progression to AIDS or death in patients enrolled during 1995-96 compared to 1988-90, the former period being one with widespread use of dual and triple therapy.[18] These improvements in mortality continued as triple therapy was further refined in general clinical practice.[19]

Cohorts following patients with known dates of seroconversion have dramatically demonstrated the temporal trends in outcomes based on the year of seroconversion, as a result of the availability of combination antiretroviral therapy. The Concerted Action on SeroConversion to AIDS and Death (CASCADE) collaboration reported in 2003 that the hazard ratio for death for seroconverters in 2001 was 0.16 compared to pre-1997 data,[20] and more recently demonstrated that the excess mortality in

patients with HIV compared to the general population has fallen from 40.8 per 1000 person years pre-1996 to 6.1 in 2004-2006.[21] Surveillance data confirm these findings. In the United States, reported deaths with HIV as the underlying cause of death have fallen from 50,000 per year in 1995 to 16,000 in 2005.[22]

Prognosis and associations with mortality

Measured from the time of starting antiretroviral therapy, in patients without prior exposure to treatment, prognosis in terms of mortality or disease progression has remained constant since the advent of three drug antiretroviral therapy.[23] Within cohorts however, prognosis varies based on patient characteristics when starting ART.[24-25] In one cohort collaboration in Europe and North America, it was estimated that in almost 50% of patients starting ART before 2007, the risk of death at five years was less than 5%.[25]

In the above settings, the characteristics most strongly associated with prognosis after adjustment for all other baseline characteristics, were age (those over 50 were three times as likely to die compared to those aged 17-29 at the start of ART), mode of transmission (those who acquired HIV through injecting drug use were at higher risk of death), clinical stage, CD4 count and viral load.[25] The association with baseline CD4 count has weakened as duration of follow-up has increased, but even with follow-up extending to five years, there is a three-fold higher mortality in those starting ART with CD4 counts below 25 cells/μL compared to those starting with CD4 counts above 350 cells/μL.[25] In the same collaborative cohort, analysed a few years previously with follow-up to three years, the adjusted hazard ratio comparing those starting ART with a CD4 count below 50 cells/μL to those starting ART with a CD4 count above 350 cells/μL was closer to five.[24] Baseline CD4 counts have been shown in the same cohort to be related to the risk of new AIDS events up to six years after starting ART.[26] The association with baseline viral load is attenuated after adjustment for other variables, but viral load has still been an important component of the above prognostic models, dichotomized at above and below 100,000 copies/mL.

Most analyses from cohorts in Europe and North America present survival stratified by baseline characteristics, and absolute survival or mortality estimates for entire cohorts are seldom presented due to the inherent differences in the characteristics of patients in each cohort and temporal changes in these, limiting comparability. For illustrative purposes, the online risk calculator based on the above prognostic models,[27] estimates cumulative mortality at years 1 to 5 for one subset of patients (treatment-naïve adults aged 30-39, sexually infected with HIV, with an initial CD4 count between 50 and 99 cells/μL, CDC stage C disease, and an initial viral load above 100,000 copies/ml), to be 3.0, 5.3, 7.2, 9.1 and 10.8% respectively.

Biological differences in HIV-1natural history and response to therapy across settings

Various data suggest that there is little reason to anticipate on biological grounds, that the response to HIV therapy should differ in Southern Africa compared to in those countries in which it was first available.

Although there is substantial strain diversity between settings for HIV-1, with subtype C predominating in Southern Africa, and subtype B in Europe and North America,[28] the current consensus is that the time to AIDS and time to death does not differ markedly between patients infected with these subtypes across regions.[29-30]

There has however been some concern that the pathways to developing resistance on treatment might be different in Southern Africa (where subtype C virus predominates) compared to patients infected with subtype B virus. For example, it has been suggested that in patients infected with subtype C viruses, resistance to NNRTI's might develop more rapidly,[31] as well as the K65R mutation in patients treated with tenofovir (TDF).[32] Nevertheless, it is generally anticipated that overall, the response to first-line therapy should not differ based on geographical viral genetic diversity.[31 33]

An increasing number of pharmacogenetic associations are being described for antiretroviral drugs.[34] These are beginning to impact on clinical practice, but to date, more in understanding toxicity than efficacy. For example, two studies have shown the utility, where resources exist, of screening for the human leucocyte antigen (HLA)

allele HLA-B*5701, which is 100% specific for hypersensitivity reactions to abacavir (ABC).[35-36] Such screening is now recommended in the International AIDS Society (IAS) USA guidelines.[37] Although hypersensitivity to nevirapine (NVP) is of more relevance than that to ABC in Southern Africa due to its more widespread use, the genetic basis for NVP hypersensitivity is more complex and diverse that that for ABC.[34] The association between reduced efavirenz (EFV) clearance and the G156T substitution in the cytochrome p450 2B6 enzyme is more clearly described,[38] and has been found to be more frequent in African populations both in North America and South Africa.[39-40]

Even though there are additionally differences in the spectrum of HIV-associated diseases between settings, the feasibility of antiretroviral therapy in Southern Africa and other poor countries was challenged on the grounds of affordability, health system capacity, and patient adherence.[41] A discussion on co-morbidities is however included in the next section.

The emergence of ART as a feasible intervention in poor countries

The literature reviewed below follows the introduction of ART in poor countries. The data are introduced with a clear sense of chronology up until the point that this thesis was proposed, in order to enable the contributions from this thesis to be located relative to the time when they were conceptualized and produced.

By the late 1990's, the effectiveness of three-drug ART was well-established as described above. The lowest annual cost in 2000 of an effective first-line antiretroviral drug regimen was however $10,439 (USD) per patient per year from originator manufacturers. Although in Brazil the same regimen was available for $2767 per patient per year produced by the state, this was not readily accessible to patients outside of Brazil. By mid-2008, the same regimen (d4T, 3TC, and NVP) was available for $331 (originator) and $87 (generic), representing price reductions of 97% and 99% respectively.[42]

In 2002, assuming already at that stage that therapy could be provided at $350 per year, it was argued that per disability-adjusted life year averted, ART was 28 times less

cost-effective than prevention.[43] There was widespread anxiety about the impact of poorly regulated use of antiretroviral therapy in Africa leading to resistance,[44-46] and early reports of successes were received with caution due to the possibility that they were anomalies, the result of extraordinary resources due to partnerships with implementing organizations.[41]

The early projects to provide ART in poorer countries were premised on assuming that with volume increases, political pressure, and reform of trade regulations, the cost of therapy could be substantially reduced,[47-48] that it was possible to simplify the model of care to enable less well-resourced health systems to deliver the intervention while retaining effectiveness,[44 49] and that it was possible to achieve adherence levels that would render the intervention effective and safe at a population level, whether by observing therapy directly,[50] or through patient education and empowerment.[51] It was also anticipated that the availability of treatment would catalyse the response to the epidemic, improving the effectiveness of all interventions.[49 51]

Against this backdrop, of assumed biological efficacy, the early projects providing ART in the region sought to demonstrate that the new models of ART care provision, different in many ways from those in Europe, North America and Brazil, could ensure adequate outcomes at individual and programme level, especially when combined with the use of more affordable generic drugs.

The first programme descriptions on 60 patients treated with ART in Haiti, were based on a project in which treatment was provided on clinical criteria, and monitoring was also restricted to clinical parameters, and were published in 2001.[49] This project popularized the use of "accompagnateurs" a cadre of community health workers responsible for assisting with treatment, an extension of the directly-observed component of the DOTS model for tuberculosis treatment.[50]

The first two publications of results from routine ART programmes in Africa were published in mid-2002. As early as 1998, UNAIDS created the Drug Access Initiative (DAI) in order to facilitate access to antiretrovirals at lower prices in selected countries. An evaluation of the pilot DAI project in Uganda, in which patients were

still responsible for their own health care costs, found that for 204 patients starting ART, survival at one year was 82% and 67% for patients starting ART with CD4 counts above and below 50 cells/μL respectively.[52] The Senegalese government had also in 1998 begun a government sponsored ART programme. In 58 patients enrolled by mid-2002 with a median CD4 cell count of 110 cells/μL, 85% remained alive and free of new AIDS events at one year.[53] Follow-up extended to 18 months. In the latter study, all patients received an un-boosted protease inhibitor (PI) as part of their regimen. NNRTI's were available in the former study, but the proportion using them was not reported. In analyses of those who received ART (as opposed to intention-to-treat analyses), virological suppression was 42% (Uganda) and 61% (Senegal) at one year in these two studies.

An evaluation in a DAI project in Côte d'Ivoire of 276 adults who received triple therapy and returned for follow-up care, estimated in 2003 that survival at one year was 84% and for the 35 patients with virological assessment around one year, 50% had viral loads below 200 copies/mL.[54] A smaller cohort study reported on outcomes for 90 patients who started three-drug ART in Côte d'Ivoire from 1996-2002, full details of which could not be accessed.[55]

A cross-sectional chart-review of 217 adult patients started on three-drug ART in private practice in Kenya from 1996-2000 reported in 2003 that 51% remained alive and in care, 8% were alive but not in care, 15% were lost to follow-up, 11% had died, and 13% had transferred or moved their care.[56] Of the 55 patients receiving a viral load test between 7 & 12 months on ART, 47% had values below 400 copies/mL. A review of 139 patients in Tunisia started on ART reported cross-sectionally that 6.4% had died and 63.5% had achieved virological suppression over a median 23 months of follow-up.[57]

A review of adherence and virological outcomes in African patients receiving ART through clinical trials in Cape Town from 1996-2001 demonstrated high levels of adherence as measured by pill-count (median 93.5%) and virological suppression (66% below 400 copies/mL at 48 weeks), and predictors of detectable viral loads that were similar to those described in other settings.[58] A public sector treatment

programme initiated by the same research group in Gugulethu in Cape Town reported virological outcomes at 16 weeks for the first 16 patients starting ART, all of whom had undetectable viral loads.[59] Médecins Sans Frontières also reported in 2003 that of 743 patients started on ART in seven countries in Africa and South East Asia, 89.5% remained alive at 6 months, and 89.8% of 118 tested at six months had undetectable viral loads (all from Khayelitsha, South Africa).[60]

The early results from Khayelitsha published in 2004, were the first detailed public sector cohort results for ART from Southern Africa. The study extended follow-up to two years, and reported on a project that was predominantly based on the use of generic drugs which had been imported from Brazil (see below).[2] All metrics in this study improved on the previously published African studies, with survival at two years of 86.3% in a population with very advanced disease at the start of ART (median CD4 count 43 cells/μL), and 89%, 84% and 70% achieving viral load suppression at 6 months, 1 and 2 years respectively. This project also popularized an adherence model premised on careful patient preparation and education, treatment assistants that were voluntary and known to the patients as opposed to employed community health workers, support groups and the encouraging of disclosing HIV status.[51 61-62]

A clinical trial in Cameroon further demonstrated the effectiveness of programmes based on the use of generic drugs. The fixed-dose combination Triomune®, comprising d4T, 3TC and NVP, was used to treat 60 patients, 80% of whom achieved virological suppression at 24 weeks.[63] This study built on a small adherence study in Uganda, which reported that for 34 patients on Triomune followed to 12 weeks, 76% had undetectable viral loads.[64]

The above studies were the only African studies identified in reviews published in 2005,[65-66] and form the backdrop to the conceptualization of this thesis in 2004 when the candidate first registered.

Proliferation of evidence as to the effectiveness of ART in African countries

The evidence as to the effectiveness of ART in Southern Africa emerged rapidly thereafter, with the dramatic expansion of ART linked to the awarding of GFATM grants, and the launch of the World Health Organization (WHO) 3x5 initiative and of PEPFAR. It is not possible or useful to chronologically and exhaustively review each incremental or parallel contribution to this evidence base. Instead, relevant studies are grouped thematically or geographically.

South Africa

In late 2003, the South African government approved a plan to routinely provide ART for treatment of HIV in the public sector,[67] implemented starting in April 2004. By March 2009, almost 700,000 patients were reported to have started ART in the public sector in South Africa. There is however a paucity of data on the effectiveness and outcomes of this national programme. A number of individual projects and provinces have however published outcome data.

The cohort in Gugulethu, Cape Town, referenced above,[59] has described patient outcomes when looking at the timing of mortality,[68-69] the contribution of cryptococcal meningitis to mortality,[70] the relationship between mortality and the most recent CD4 count,[71] the role of viral load monitoring,[72] the effect on outcomes of increasing patient enrolment,[73] and the associations with mortality.[74] The project has developed a lay health worker model for patient support, and is one of the best followed cohorts in South Africa. Although loss to follow-up is not formally accounted for, the longest follow-up reported to date was 4 years, at which duration 13.2% of patients had died.[71]

The Free State province has tracked all patients enrolled into HIV care in the public sector in a common monitoring system, and was able to report on the early outcomes for all HIV-infected patients as well as those starting ART.[75] The availability of data for all patients enabled an analysis similar to the one described above in the Swiss HIV Cohort Study,[15] in which the effectiveness of ART compared to no ART could

be estimated. ART was associated with an 86% reduction in mortality. Additional striking findings were that in the period of follow-up (2004-2006), 53% of patients died, 87% of whom had not started ART, and 80% of the deaths were only ascertained on the basis of linkage to the national death registry. Virological outcomes were not reported.

McCord Hospital is a state-aided hospital in Durban, at which patients pay a small and all-inclusive co-payment. An analysis of outcomes for 309 patients demonstrated the associations between disease advancement and mortality.[76] Cross-sectionally over a mean follow-up of 257 days, 16% of patients had died and 7.4% had been lost to follow-up. Virological outcomes were not reported.

The Western Cape Province has described outcomes at scale across the entire province based on the routine monitoring system in place in the province.[77] This analysis incorporates data from both Khayelitsha and Gugulethu. In a combined cohort of 12,587 adults, 72% remained alive and in care at four years. There was a parallel decline in early mortality and increase in loss to follow-up over time. Virological suppression to below 400 copies/mL was 85% or higher throughout follow-up. The Khayelitsha cohort has been able to use death registry linkages as was done in the Free State province, to robustly describe patient survival and temporal trends in outcomes for over 7,000 patients. Both of these analyses form part of this thesis, describing the effectiveness of ART in this setting over longer durations and at scale in a provincial health service.

Whereas ART has only been available in the public sector in South Africa in recent years, it has been available in the private sector since before the era of triple therapy. An analysis of one of the largest private sector cohorts demonstrated that for 6288 patients started on ART by March 2003, 3.5% had died, and 18% had been lost to follow-up.[78] There was a strong relationship between the proportion of pharmacy refills collected and survival. This relationship was subsequently described with the probability of sustaining viral load responses in patients starting on NNRTI regimens.[79] In patients who collected all of their drugs, 73% had continued viral load suppression throughout follow-up. This and a subsequent study demonstrated more

favourable viral load outcomes for patients on EFV compared to NVP.[80] Workplace programmes in South Africa have similarly demonstrated the effectiveness of ART since 2002, with good viral load results, but a high proportion stopping treatment over and above those who died.[81]

Other African settings

Botswana was the first country in Southern Africa to launch a national treatment programme, with treatment beginning at Princess Marina Hospital in Gabarone in 2001.[82-83] The programme started with a regimen based on a NRTI backbone of d4T and ddI which would later no longer be recommended for first-line therapy, together with an NNRTI. Viral load monitoring is provided in Botswana, the only other country in the region besides South Africa to routinely provide this. In a cohort of 153 patients starting ART in 2001-2002 at Princess Marina Hospital, survival and virological suppression were as anticipated from earlier studies, and a high proportion (32%) had changed therapy due to toxicity on this regimen.[82] Poor programme monitoring has resulted in few data being available on the effectiveness of the Botswana national programme, although a retrospective chart review of 633 adults started on ART by the end of 2002 and followed until April 2007 demonstrated good longer term (five year) outcomes whereby 21% of patients had died and 22% were lost to follow-up.[84] Established measures of disease advancement were confirmed to be associated with mortality.[85] Despite the lack of programme-level data on effectiveness, reviews of national mortality data in Botswana, where vital registration is considered good, demonstrated a decline in mortality in adults aged 25-54 coinciding with the rapid expansion in the national ART programme (2003-2005).[86]

Malawi developed a comprehensive and context-appropriate national programme for ART, informed in part by experiences in the national tuberculosis programme,[44 87] and donor-assisted initiatives in the Thyolo and Chiradzulu districts.[88-89] Although the cohort monitoring system in use has been the benchmark for the WHO,[90-92] adult outcomes of the country programme have only been reported as cross-sectional,[91 93] or at one year duration on ART.[94-96]

Whereas the Chirudzulu programme reported 76% of patients retained in care at one year,[89] the national programme reported 81% alive and in care over a much larger cohort tracked through the paper-based monitoring system.[94] A viral load survey of 334 patients on ART for 6 months or more in the Chirudzulu programme showed 84% of them to have values below 400 copies/mL.[89] A separate study reporting on the outcomes in patients lost to follow-up (9% at one year)[94] reported that half had died and an additional quarter could not be traced.[97] Sub-analyses have demonstrated that patients starting ART on concurrent treatment for tuberculosis have equivalent or better outcomes (survival, retention and CD4 count response) than those not on treatment for tuberculosis,[95] and inferior outcomes for patients starting ART with concurrent Kaposi's sarcoma.[98] A demographic surveillance system was able to identify a small decline in adult mortality soon after the introduction of ART in Malawi,[99] although this estimate was based on very few averted deaths.[100]

In Zambia, 21,755 adults were enrolled onto ART in the space of 18 months beginning in April 2004.[101] This project reported outcomes at one year, demonstrating successful rapid scaling up of care, the same risk factors for mortality as above, and confirming that most of the mortality occurred early (71% in the first three months). Patients accessed care earlier than the South Africa cohorts described above (median CD4 count 143 cells/μL at enrolment), and in keeping with other Southern African cohorts, more women than men accessed ART (61%). This programme has also demonstrated success in shifting clinical care from doctors to clinical officers and nurses.[102]

In West Africa, the Senegalese government programme described above reported updated results at 3 and 5 years on ART for those enrolled by April 2002.[103-104] [105] Reporting on 404 patients, a quarter had died at five years, not accounting for loss to follow-up which was not estimated beyond two years.[104] The Triomune trial in Cameroon demonstrated sustained efficacy at 24 months duration, although viral load suppression to below 50 copies/mL (versus below 400 copies/mL) was considerably lower at 24 months compared to 12 months (64% vs. 79%, as-treated analysis). Treatment was changed due to toxicity in only 2 out of 60 patients.[103]

In Côte d'Ivoire, the ANRS 1203 cohort in Abidjan (later known as Cotrame and then CEPREF) which was one of the early cohorts to report on outcomes as described above,[55] provided updated estimates of the effect of ART on mortality,[106] severe opportunistic infections,[107] tuberculosis,[108], and morbidity events.[109] During the rapid scale up of treatment post 2004 in this and related cohorts, 18 month mortality was 15% with an additional 21% of patients lost to follow-up for 3 months or more.[106]

In Uganda in East Africa, a cross-sectional virological survey (median duration on ART of 38 weeks, 137 patients) found 66% of patients to be virologically suppressed, with unplanned treatment interruptions independently associated with non-suppression.[110] In a rural clinic in Mbarara, Uganda, mortality estimates were corrected with data from patients who were lost to follow-up and subsequently traced, yielding a cumulative mortality estimate at 3 years of 12.2%.[111] An observational study and later a clinical trial run by the The AIDS Support Organisation (TASO) in Uganda have both demonstrated very effective home-based ART interventions.[112-113] Excellent adherence in patients receiving home-based ART has separately been demonstrated in Uganda.[114] In a research cohort of 559 ART-naïve adult patients nested into the programme run by the Infectious Diseases Institute at Makerere University, 17% of patients died overall, with mortality declining with duration on ART from 17.9 deaths per 100 patient years in the first year to 1.2 deaths per 100 patient years between two and three years on ART. The majority (86% of first year deaths) were considered HIV-related. Four deaths (7%) in the first year were attributed to immune reconstitution inflammatory syndrome (IRIS), and all to unmasking as opposed to paradoxical IRIS. Cumulative mortality for the whole cohort was not presented, but stratified by CD4 count, appeared similar to other cohorts in the region. Patients with CD4 counts below 25 cells/μL at ART initiation were at particularly high risk of death, with over 25% having died by 3 years.

In Western Kenya, the Academic Model for the Prevention and Treatment of HIV/AIDS (AMPATH) project has seen a rapid scaling up of ART provision. The project reported in 2006 on a cohort of over 2000 adults started on ART.[115] Overall

5.4% of patients had died (cross-sectionally, i.e. all deaths at the time or reporting divided by all patients who ever started ART in the study period, irrespective of duration of follow-up), and cumulative loss to follow-up (3 months without a visit) was 30% at two years on ART. The project was later able to demonstrate in over 23,000 patients how rapid scaling up had resulted in patients accessing ART with less advanced disease.[116]

Collaborations

There have been important contributions from collaborations based on cohorts in resource-limited or African settings. These analyses are included in relevant sections below, but are briefly summarised in this section.

The Antiretroviral Therapy in Lower Income Countries (ART-LINC) collaboration[117] was instrumental, through comparative analysis with a longstanding collaboration from wealthier countries, in demonstrating differences in early mortality on ART between settings.[118] The collaboration included many African and in particular Southern African cohorts, in addition to cohorts in Brazil, Thailand and India. Subsequent analyses have demonstrated that the relative decline with duration on ART in tuberculosis case-finding is comparable across settings in spite of higher case-finding in lower-income countries,[119] and that women in Southern Africa are not disadvantaged in their access to ART compared to estimates of need.[120] The scale-up of ART in the region was reflected in the collaborative database,[121] as was the increase of loss to follow-up with increasing scale-up, together with the associations of fee-for-service and low baseline CD4 counts with loss to follow-up.[122] The collaboration has described the evolution of CD4 count on ART,[123] and has demonstrated the poor performance of CD4 count measures at predicting virological failure.[124] In participating cohorts with viral load monitoring available, switching to second-line regimens occurred earlier and at higher CD4 counts than in cohorts without viral load monitoring.[125]

The majority of the Southern African cohorts which participated in the ART-LINC collaboration now contribute data to the International Epidemiologic Databases to Evaluate Aids (IeDEA) Southern Africa collaboration. Important contributions to

date from this collaboration include the description of treatment-limiting toxicities in South Africa that forms part of this thesis,[126] the comparison of outcomes in the public health approach to ART as applied in South Africa to outcomes in the Swiss HIV Cohort Study,[127] and the comparison of mortality on ART to background mortality in selected sub-Saharan African countries.[128]

Clinical and programme design considerations

The above sections have detailed the emergence of data on the effectiveness of ART as it has emerged in South Africa and the region, as well as other African countries.

Reviewed below are clinical or programme design issues related to the provision of ART in these settings, and draws together studies from different countries and settings. As the papers included in this thesis have been prepared and published over a period of rapid advancement in our understanding of treatment in this region, some of the thesis findings form part of this review.

Loss to follow-up

As mentioned at the end of the previous section, cohort attrition due to loss to follow-up has emerged as a major challenge to assessing cohort performance in Africa.

Traditionally in high income countries, loss to follow-up has been treated as a censoring event in survival analyses. Studies have however demonstrated that patients lost to follow-up in these settings do have inferior survival and laboratory outcomes.[129]

It was not surprising that as ART programmes have expanded where health systems are weak and patients experience substantial barriers to accessing care, an increasing number would be lost to follow-up. This has been demonstrated succinctly in the Western Cape looking at early loss to follow-up which has increased while early mortality has declined.[77] A review of treatment programmes with published outcomes up to two years on ART presented a view that published outcomes were

unrealistically optimistic due to loss to follow-up, estimating that 40% of patients were lost to care (including deaths) by two years.[130]

In response it was pointed out that varying definitions were used for defining loss to follow-up. Typically, the convention has been to define loss to follow-up as patients not being seen for two consecutive clinical visits. In high income settings, stable patients are usually seen 6-monthly, hence the use of 12 or 13 months to define loss to follow-up. This was the definition initially proposed in a collaborative analysis from resource-limited settings.[118] Other studies have used 3 months without a visit,[77] demonstrating the wide variability in this definition.

Follow-up studies have powerfully demonstrated that a high proportion of patients lost to follow-up in these settings have in fact died, ranging in African studies from 12% to 87%.[97 131-134] In settings where services are based in the community through primary care clinics, retention in care is generally better than for large hospital-based programmes.[135-136]

Statistical approaches are developing to correct mortality estimates in the context of loss to follow-up. Some are based on multiple-imputation,[128] and others, sometimes termed "double-sampling", are based on the outcomes from exercises to trace patients lost to follow-up.[111 137] While it is widely anticipated that reported mortality is an underestimate of true mortality, a double-sampling based correction has demonstrated this to be the case in a Ugandan cohort.[111]

Early mortality and comparative studies

Many early reports from ART programmes in Africa drew attention to the high early mortality (in the first 3 or 6 months on ART),[2 52] but still considered the outcomes to be comparable to those for very ill patients in high income countries. A comparative study, which included two cohorts from the Western Cape, was able to adjust for degree of illness, and reported that after adjustment, mortality was higher in resource-limited settings in the early months on treatment (adjusted hazard ratio [AHR] 4.3 in the first month, and 1.5 for months 7-12).[118] The confidence intervals beyond 6 months were wide, but a subsequent comparison of the two Western Cape cohorts to

the Swiss HIV Cohort Study reported AHR's for mortality of 5.9 and 1.8 for months 1-3 and 4-24 on ART respectively.[127] Standardised mortality ratios (SMR's) comparing mortality on ART to background mortality in the general population in resource-limited settings have also demonstrated the excess mortality soon after starting ART compared to longer durations on treatment: for patients initiating therapy with less advanced disease and a CD4 count above 200 cells/μL, the SMR fell from 30.2 to 1.1 comparing months 1-3 on ART to months 13-24.[128]

Explanations offered for this higher early mortality include the high prevalence of tuberculosis and immune reconstitution inflammatory syndromes (eg. to tuberculosis and cryptococcal pathogens), limited acute care capacity, and the late presentation of patients with respect to disease advancement.[69] [127] Mortality declines have occurred in parallel to progressively earlier ART initiation, but it has not been known if these are fully predicted by measured improvements in baseline CD4 count and clinical stage.[77]

Regimens

Most African ART programmes are based on a first-line regimen consisting of two NRTI's and an NNRTI. The NRTI's most commonly used are d4T and 3TC, in combination with NVP or EFV. One of the reasons for the widespread use of this NRTI combination with NVP is their availability as a single tablet fixed-dose combination.[63]

The d4T/3TC combination has been shown to be as effective as other NRTI combinations such as TDF/3TC.[138] In high-income countries however, the most commonly used NRTI combination is TDF/FTC, which outperformed AZT/3TC when combined with EFV on virological, immunologic and safety measures.[139] The use of this combination has been boosted by the availability of a once-daily single tablet fixed-dose combination of TDF/FTC/EFV, which is increasingly the initial antiretroviral regimen of choice in high-income countries. The main obstacles to the wider use of this regimen in African programmes are the cost (generic products are only beginning to emerge),[140] contra-indications to EFV use (pregnancy or pregnancy risk), and concerns about the need for renal function monitoring in patients on TDF. TDF has however been shown to have a similar renal safety profile to d4T,[141] and

long term small declines in glomerular filtration rate over time have not been considered clinically relevant.[142] Studies in African settings have shown that ART generally improves renal function in patients who begin therapy with renal function impairment,[143] and where comparison with TDF containing regimens was possible, observed deteriorations in creatinine clearance were not associated with the regimen.[144]

Greater concerns have been expressed however about the toxicity profile of d4T rather than virological inferiority.[126 145-153] In particular, life-threatening lactic acidosis, already known to occur more frequently in patients on d4T compared to other NRTIs,[154] has been demonstrated to occur much more frequently in Southern Africa,[126 145 147 152] and in particular in women with high body weight or mass indices at the start of ART.[126] International guidelines were changed to avoid higher doses of d4T based on evidence of lower toxicity risks with retained efficacy.[155] The impact of this guideline change on toxicity is not yet known. Symptomatic hyperlactataemia and lactic acidosis are rare before six months on ART, and one strategy proposed has been to initiate ART with d4T, and routinely substitute d4T with AZT after six months of therapy.[156] It is argued that this strategy could potentially minimize the toxicity risks of both drugs, since AZT-related anaemia is less common in patients initiating AZT-based ART with higher CD4 counts, and substantial recovery in immune function is anticipated by six months on ART.[157] It would however require closer clinical or laboratory safety monitoring after six months of ART when for many stable patients clinical visits are already three or more months apart.

The preferential use of NNRTI's compared to boosted protease inhibitors (BPI) for first-line regimens in the region is based on cost, stability and efficacy. EFV has been shown to be superior to lopinavir/ritonavir[158] or amprenavir/rionavir[159] in terms of time to virological failure. There was a greater increase in CD4 count in the BPI group in the former study, the clinical importance of which was unknown. Regarding the choice of NNRTI, NVP use has predominated in the region for many of the same reasons as the use of d4T – it is frequently co-formulated in a cheap generic fixed-dose combination.[42] In South Africa however, EFV is more often used than NVP as the NNRTI in first-line regimens as clinicians are free to select either, and

the regimens are not provided as fixed-dose combinations, eliminating one of the major advantages of NVP-based regimens. As concerns efficacy, clinical trial data initially failed to demonstrate inferiority of NVP compared to EFV,[160] although for the South African participants in the 2NN trial, virological responses were inferior for those receiving NVP. A number of cohort studies have subsequently demonstrated inferior virological outcomes for patients on NVP compared to EFV in both high income[161-165] and low and middle-income settings.[79 105 166-168] This difference may be accentuated when patients are concurrently on tuberculosis treatment when starting NVP-based ART,[166 169] which is frequently the case in countries where access to EFV is limited. Concerns have also been expressed that overweight patients on NNRTI's may be particularly susceptible to sub-therapeutic drug levels.[166 170-171]

Although a much wider range of antiretroviral agents are available, including abacavir, these are not discussed further as they have not featured prominently in considerations for optimal regimens in resource-limited settings. There was a time when regimens containing three NRTI's were considered a good option as this spared an additional class of agents for subsequent regimens, but this has faded with the evidence of inferior outcomes with this strategy.[172-175] Regimen options for second and third-line regimens in the region are also not discussed further.

Other associations with virological response

Measures of disease severity at the start of ART have been identified for many years to be associated with higher risks of virological failure, including a high initial viral load,[162 164 176-177] low baseline CD4 count,[164 176] and a previous AIDS diagnosis.[164] These have been confirmed in Southern Africa for viral load and CD4 count.[79 166 178] Younger age[166 177 179] and current CD4 count[177] have further been associated with virological failure, whereas gender has not generally been found to be associated with failure.

Factors influencing adherence have been found to be associated with virological failure in South Africa, including the language of the service provider, and higher dosing frequencies.[58] Adherence measures where available, have been confirmed to

be associated with virological failure in Southern African (pharmacy refill)[79 180] and Brazil (self-report).[181]

Clinicians have long been concerned that abruptly stopping NNRTI-based therapy places patients at risk of a period of NNRTI monotherapy due to the relatively long half-life of NVP and EFV. Cohort studies have supported this concern, [182-183] and unplanned treatment interruptions have been found to be associated with viraemia in patients on ART in other African settings.[110] A similar mechanism is operative when pregnant women receive NVP at the onset of labour as part of prevention of mother-to-child transmission (PMTCT) interventions, where the long half-life of NVP is linked to NNRTI resistance.[184]

Studies looking at the clinical impact of this resistance post PMTCT first demonstrated that virological outcomes at 6 months were inferior in women exposed to single dose NVP (SD-NVP).[185] It was subsequently demonstrated that women in whom there had been a delay of 6-18 months between SD-NVP and starting ART responded as well to NNRTI-based ART as unexposed women.[178 186-187] Additional antiretrovirals antenatally,[188] as well providing additional antiretroviral coverage post-natally to cover the relatively longer half-life of NVP, have both been demonstrated to reduce NVP resistance, but have not been tested with respect to subsequent clinical response to ART.[189]

Immunological responses

Estimates as to the ability of HIV-infected individuals to quantitatively restore immune function through CD4 count recovery have been constantly upgraded. As early as 2003, cohorts in Europe and North America reported on CD4 count recovery in patients with sustained virological suppression, reporting at the time that for all groups of patients, recovery was still continuing at 3 and 4 years respectively.[190-191] Nevertheless it has long been established that there is a small subgroup of patients who have limited immunological recovery in spite of virological suppression, most commonly due to a blunted initial response to therapy.[192-193]

Within the natural variation of response, a third of virologically suppressed patients in the Swiss HIV cohort had not attained a CD4 count above 500 cells/μL by 5 years on ART. Lower CD4 counts in the first six months on ART, older age, and starting with a lower CD4 count were all associated with failure to attain this response.[194]

Updates to these estimates have been slightly divergent with respect to continued CD4 count recovery. One analysis identified a plateau in absolute CD4 count in virologically suppressed patients, at all strata of baseline CD4 count, at 5 and 6 years duration on ART,[195] whereas another found that on average, patients from all strata were still accumulating CD4 cells beyond 5 years on ART.[196]

African studies have not generally been able to examine CD4 count responses on the basis of virological suppression, due to viral load measures not being available. One collaborative study without the benefit of viral load measures (which included data from Khayelitsha), found evidence of plateaus being reached, more marked for patients starting ART with very low CD4 counts.[123]

Due to the much lower starting CD4 cell counts,[118] even with equivalent recovery, patients in this setting spend a much higher proportion of time with lower CD4 counts, placing them at greater risk of morbidity and mortality.[197]

Monitoring the response to therapy and switching therapy

The approach to monitoring therapy has evolved with the development of drugs and technology, and in well-resourced settings, the International AIDS Society recommendation is for stable patients to have frequent viral load tests (every 3 to 4 months), in concert with CD4 count tests until the CD4 count is consistently above 350 cells/μL, after which the CD4 counts could be done less frequently.[37] Viral load monitoring more frequently than 6-monthly is supported by a clinical trial with respect to viral load outcome, and possibly survival,[198] whereas a cohort study reported a low risk of treatment failure in stable patients in whom it may be safe to space the tests further apart.[199]

In the above guidelines, patients with confirmed viral loads above 50 copies/mL meet the definition of treatment failure.[37] If the level of viraemia is above 500 copies/mL, resistance testing is considered "essential".[200]

This contrasts markedly with many African country programmes, where the resources for regular viral load monitoring are not available, and WHO, recommendations for resource-limited settings do not recommend routine viral load monitoring.[201] Nevertheless, many clinicians in these settings still consider virological monitoring to be the goal, evidenced by the plethora of studies demonstrating that immunological failure criteria, however constructed, are a poor proxy for virological failure.[202-206]

Recent evidence demonstrating that earlier initiation of ART than previously recommended,[207 208] as well as avoidance of treatment interruptions, are associated with improved clinical outcomes,[209-211] are lending support to the view that viraemia, independent of immunological status, is harmful to patients.[212]

The alternate position, is that identifying virological failure early may not necessarily result in improved programme-level outcomes given the limited number of drugs and regimens available. It is based on evidence that low grade viraemia (around 4 $\log_{10}$ copies/mL) can support immunological stability or further recovery,[213-220] and the argument that second-line regimens may still be highly effective in spite of resistance to the first-line regimen.[221]

This view has been leant support by a modelling study which did not find benefits to viral load monitoring with the current regimens in use in most African settings,[222] whereas another study has found that for patients on NNRTI's as opposed to BPI's, CD4 count decline is more likely with low-grade viraemia.[223] The only clinical trial to formally seek to address the optimal timing of treatment switching was unable to complete enrolment, due to the very widely held view amongst clinicians and patients in favour of early switching.[224]

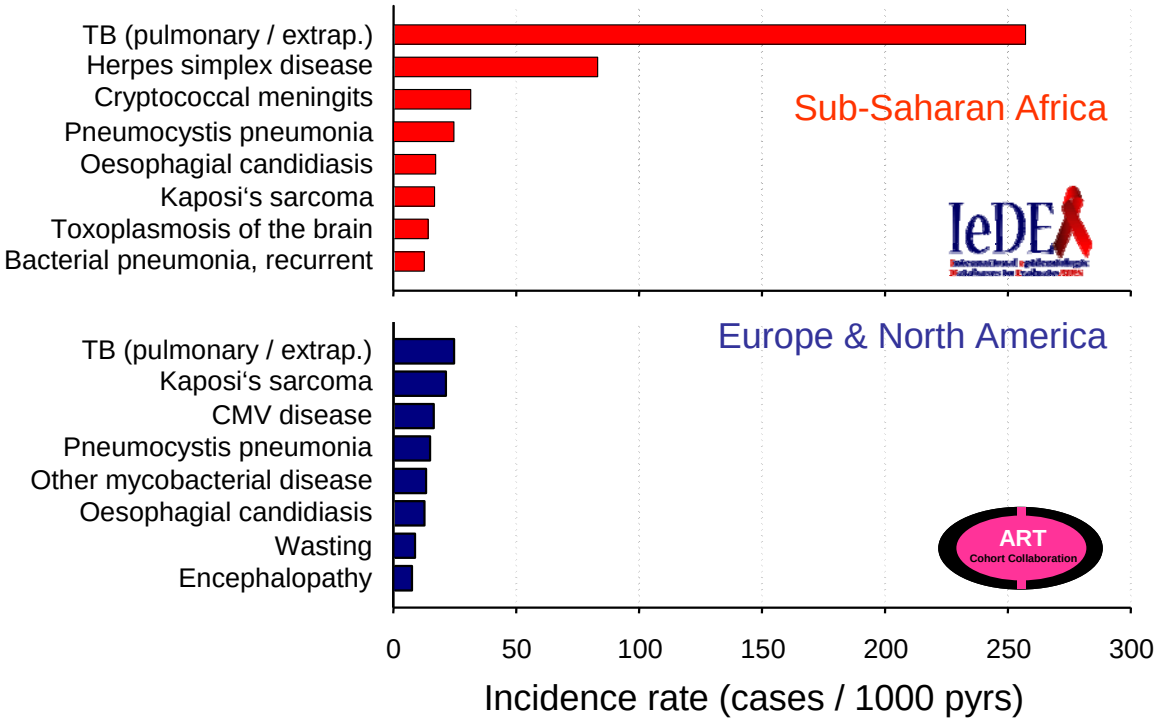
The resistance consequences of delayed switching in the context of a public health approach are demonstrated by studies from Malawi and South Africa.[225-226] In the

Malawi programme, switching is guided by CD4 count criteria. At the time of switch, the majority of patients had treatment-limiting resistance to 3TC (81%) and NNRTI's (93%) as anticipated. In addition, 56% of patients had thymidine analogue mutations (TAMS), of whom 44% had three or more TAMS. Unexpectedly 23% of patients had mutations conferring resistance to TDF. In the South African national ART programme by contrast, where switching is based on confirmed viraemia above a threshold of 1000 or 5000 copies/mL, whereas there was also a high frequency of mutations conferring resistance to 3TC and NNRTI's (78% and 86% respectively), there was a much lower proportion with TAMS (23%), and those with TAMS had fewer mutations (20% had two or more TAMS).[226] Nine percent of patients in this study had the K65R mutation limiting future treatment with TDF, ddI or ABC. The switching strategy in the South African programme when applied diligently, is therefore more likely to preserve efficacy of recycled or substituted thymidine analogues in the second-line regimen than strategies based on CD4 count criteria alone (97% without 3 or more TAMS compared to 75%).

Arguments in favour of viral load testing in resource-limited settings are also based on the value of viral load testing as an early warning sign of adherence difficulties,[72] [227] and on the assumption that increased demand will lead to technological improvements and more widespread availability and affordability of viral load testing. Stratification of patients based on viral load might enable more efficient use of resources for patient follow-up and monitoring.

Co-morbidities

One of the contextual factors differentiating HIV treatment in Southern Africa from the epidemic in wealthier countries, is the unique spectrum of HIV-associated illnesses diagnosed during treatment, in particular the much higher incidence of tuberculosis disease in resource limited settings (Figure 1). Although tuberculosis is the leading opportunistic infection in the first three months on ART in both settings, the absolute incidence in this period is about 10 times higher in resource limited settings. The other notable diagnosis with high mortality in resource limited settings that features less prominently in wealthier countries is cryptococcal meningitis.



Source: Egger 2007 [228]

Figure 1. Incidence of HIV-associated conditions in the first 3 months on ART

Overall tuberculosis case-finding exceeds 300/100,000 patients in Southern Africa, compared to less than 50/100,000 in most of Europe and North America. The annual risk of tuberculosis in HIV-infected individuals with advanced immuno-suppression approaches 30% in some settings.[229] The estimate of the incidence rate ratio for being diagnosed with tuberculosis in Southern Africa comparing patients with HIV to those without was previously reported as 6,[230] but more recently has been estimated to be much higher (20). [231]

In Khayelitsha and many parts of the region, tuberculosis is one of the major entry points into HIV care and ART, evidenced by 40% of patients starting ART in 2007 already being on treatment for tuberculosis.[166] The high level of co-infection around the time of patients first being found to be eligible for ART leads to a number of areas of clinical uncertainty, including: the timing of initiating ART in patients recently started on treatment for tuberculosis; the optimal antiretroviral regimens to be used; how best to improve the diagnosis of tuberculosis when a high proportion of patients with pulmonary symptoms do not have acid-fast bacilli on standard

sputum smear microscopy; and, whether or not there are adjunctive interventions to ART which might further reduce the risk of tuberculosis.

Antiretroviral therapy has been found to reduce the risk of tuberculosis. Compared to HIV-infected patients not on ART, the risk reduction has variously been reported as 82% and 39%, with a variety of methodological approaches employed in the analyses.[75 232] Duration of ART has been found to reduce the relative risk of tuberculosis disease similarly across settings in spite of the very different baseline incidences.[119] There has been concern that even after some years of ART, there is a substantial proportion of patients who remain at a high risk of new or repeated tuberculosis disease.[233-234] There is observational evidence that isoniazid preventive therapy in addition to ART is effective at further averting tuberculosis episodes.[235-236]

Although tuberculosis immune reconstitution disease has been found to be relatively common, especially in patients with advanced HIV disease, it has not to date been considered a major driver of early mortality on ART.[237-238] Patients with diagnosed tuberculosis who start ART have variously been reported to have similar or improved outcomes to those without tuberculosis in adjusted[166] and unadjusted[95] analyses, and higher mortality in unadjusted analyses.[239] Autopsy studies and mortality reviews however still identify tuberculosis as a major contributor to HIV-associated mortality in Southern Africa, and to early mortality on ART.[240 69 241] Unrecognised resistance to tuberculosis drugs has been identified as an important reason for clinical deterioration in hospitalised patients with HIV-associated tuberculosis.[242]

Cyrptococcal immune reconstitution disease and incident events have also been implicated as an important cause of morbidity and mortality on ART in Southern Africa.[69-70 243-244] Recent evidence suggests that patients at risk of this can be readily identified through serological antigen screening prior to ART initiation.[245]

Aim and Objectives

The first part of the above review outlines the evidence that existed as to the effectiveness of ART in the region at the time that this thesis was conceptualised. It is against this backdrop that the aims and objectives of this project were developed. The above review has also reflected on the evolution of this evidence base, as well as some of the more detailed clinical questions, based on studies that have overlapped with those included in the thesis.

The aim of this thesis at the time of conceptualisation was to describe the clinical outcomes, determinants of outcomes and scalability of the Khayelitsha antiretroviral treatment programme

Specific objectives were:

1. to describe the survival and related proximate outcomes of ART in Khayelitsha, and determinants thereof
2. to describe the tolerability and durability of drug regimens used in Khayelitsha and the Western Cape Province
3. to describe the impact of concomitant tuberculosis on ART treatment outcomes
4. to explore the effect of ART availability in Khayelitsha on the risk behaviour of those not on ART
5. to describe the Khayelitsha population in detail in order to be able to relate the Khayelitsha experience to other treatment contexts in the region
6. to determine the scalability of ART within the Western Cape Province

Section C: The Khayelitsha and Western Cape Programmes

Background to Khayelitsha

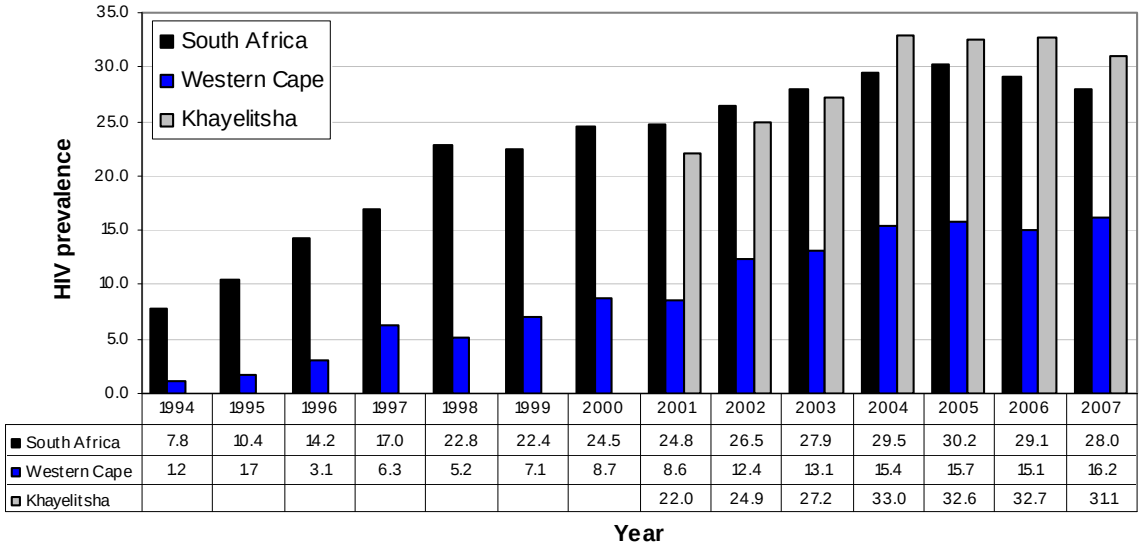
The Khayelitsha HIV treatment programme and later ART programme were set up as strategic projects by the international non-governmental organisation Médecins Sans Frontières (MSF). Soon after combination ART as described above had revolutionised HIV treatment in wealthy countries, activists had noted the potential for patients in those countries hardest hit by the HIV pandemic to benefit, and the global inequities inherent in their not being able to access ART. The MSF initiative was located in Khayelitsha by chance – the head of the mission had, on arriving in South Africa in 1998, sought South African National Department of Health approval for a project which he initially envisioned would be in Gauteng. Such approval was never forthcoming at a time when already there was political confusion in South Africa as to the role of antiretrovirals in addressing HIV. In the Western Cape however, there was at the time a government initiative in Khayelitsha to reduce mother-to-child transmission of HIV through the provision of AZT to pregnant mothers. MSF were initially invited to provide technical support to this initiative and established a base in Khayelitsha in 1999.

Khayelitsha is a relatively young township, formally established in 1985 towards the end of apartheid. There are very widely divergent estimates of how many people live in Khayelitsha, but a verification exercise in 2005 estimated the population then to be 400,000.[246] For the past decade the health care infrastructure has been relatively static, comprising three provincial government run community health centres, and 8 local government clinics. The community health centres provide acute and chronic care, and generally have a doctor available. Two of the three have emergency units, and one is open 24 hours a day for emergencies. There is no hospital within Khayelitsha, and patients requiring hospitalisation are transported by ambulance to either G F Jooste or Karl Bremer Hospitals (15-20 km). The local government clinics predominantly provide child health and tuberculosis care. The clinical staff are nurses with occasional support to the tuberculosis programme from sessional doctors.

HIV in Khayelitsha

The Western Cape began tracking district level antenatal HIV seroprevalence in 2001 (Figure 2). It appears as if the Khayelitsha epidemic may have lagged slightly behind the national epidemic at this point, and may have peaked slightly higher than the national average for pregnant women, notwithstanding the difficulties in interpreting the national antenatal HIV seroprevalence data.[247]

The comparisons within the provincial data are more robust however, due to a consistent probabilistic sampling approach throughout.[248] Khayelitsha has always represented a district of very high HIV prevalence relative to the provincial average.



	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
South Africa	7.8	10.4	14.2	17.0	22.8	22.4	24.5	24.8	26.5	27.9	29.5	30.2	29.1	28.0
Western Cape	1.2	1.7	3.1	6.3	5.2	7.1	8.7	8.6	12.4	13.1	15.4	15.7	15.1	16.2
Khayelitsha								22.0	24.9	27.2	33.0	32.6	32.7	31.1

Figure 2. National, provincial and sub-district HIV antenatal seroprevalence 1994-2007

The establishment of dedicated HIV treatment services in Khayelitsha

Dedicated HIV clinics were set up by MSF in 2000 in the three community health centres in Khayelitsha. MSF initially employed one doctor, one nurse and two counsellors per clinic, and provided drugs commonly used for HIV care. The clinics were located in space provided by either the provincial or local government, and in instances where patients required drugs that were not HIV-specific, these were obtained from the community health centre pharmacies. From inception patients have not paid any fee or co-payment for care.

From April 2000 to May 2001, the focus in the new clinics was to establish continuity of care, and treatment of opportunistic infections. Some medicines such as acyclovir for treating acute herpes simplex virus infections, had not previously been generally available prior to MSF's involvement. During this time the initial protocol for ART was developed, drawing extensively on local expertise in the research and private sectors where ART had already been available for some time, and on other initiatives within MSF, such as in Thailand where a similar protocol had been developed. ART was introduced as a research project with the following stated objectives:

> The prime objective of this project is to offer comprehensive care for HIV to a cohort of people with HIV/AIDS and show that the use of combination antiretroviral therapy **in a primary health care setting in a resource-limited environment is feasible, affordable and reproducible.**
>
> As such, this project seeks to develop a model of care for people with HIV/AIDS that can be widely adopted, including by government. For the project to be a suitable model for the government, it must achieve several key goals in the context of limited resources (including limited laboratory capacity):
>
> - Reductions in AIDS-related morbidity and mortality, and improvements in quality of life;
> - Practical feasibility of using such interventions at the primary health care level;
> - Social acceptability of introducing complicated combination therapy in a community characterized by a lack of stable institutions;
> - Economic feasibility, through an analysis of the clinical cost-savings associated with the use of antiretrovirals.
>
> As a second objective, **the pilot project aims to demonstrate that it is possible for developing countries to provide affordable care for people with HIV/AIDS immediately through the use of low-cost antiretrovirals, whether generic or patent-protected.**

> Direct importation of generic drugs would provide a powerful example to governments in developing countries of how they can affordably and sustainably confront the problem of treating people with HIV/AIDS.

This protocol sought to treat 180 patients. The first patients were started on ART in May 2001. The initial first-line regimen comprised AZT/3TC in a fixed dose formulation, and NVP or EFV if NVP was contraindicated. AZT, 3TC and NVP were imported from the Brazilian state manufacturer FarManguinhos from the beginning of 2002, continuing into 2004 until all drugs were available from the provincial drug depot. The clinical aspects of the early protocol were very similar to the current provincial protocol, with the addition of an extra viral load test at 3 months on treatment, and baseline viral load tests for everyone.

Early on in the project there was a strong emphasis on social eligibility criteria including the signing of a "contract" with the service providers, receiving a home visit, disclosing HIV status to a confidant who could provide support, and joining a support group. Alongside these criteria was a formal selection process in which all of these social eligibility criteria would be evaluated.[51]

Evolution of the HIV services in Khayelitsha

By late 2002 the project had already increased the target number of patients to 400. The Western Cape Province was also actively raising funds for treatment, including receiving support from the GFATM, agreeing with MSF to fund additional treatment beyond the 400 patients initially agreed to. This resulted in a rapidly growing and changing project.

In terms of staffing, a second nurse was added to each clinic soon after ART was first provided, followed thereafter by an additional doctor and nurse at each clinic, and additional counsellors. The Provincial government began in 2004 to create posts for medical officers and nurses, and also to rotate community service doctors through the HIV clinics. Government indirectly also took over the funding of counsellors through a government sponsored NGO. At this time there was a shift towards more

doctor-based care than had initially been envisaged by MSF due to the provisioning of medical officer posts ahead of nursing posts. By 2006 MSF's contribution to staffing the original three clinics consisted of two doctors filling in as required when there were staffing shortages. At the same time however, MSF was supporting the local government clinics to introduce ART. There have been a few clinicians who have remained in the HIV services in Khayelitsha throughout this period, but for the most part, there has been a reasonably high turnover of staff, especially when compared to other HIV services in the province.

There were subtle trends in clinical practice throughout this period. There was a shift towards more widespread use of EFV over NVP in 2002 and early 2003, after which a concerted effort was made to use NVP in preference to EFV in order to reduce costs, and enable the potential use of a NVP-containing fixed-dose combination which was anticipated in the public sector, even though it was never made available on the national tender. D4T replaced AZT in the starting regimen in late 2003 in anticipation of the national programme which provided for d4T use. Around this time (late 2003, early 2004), NVP was also used by some clinicians concomitantly with tuberculosis treatment based on the available evidence at the time, a practice continuing until late 2005. The baseline viral load was dropped for treatment-naïve adults in 2005, as well as the 3 month viral load, in order to align with practices in other clinics.

Antiretroviral therapy in the Western Cape

By the time the national ART programme was formally started in April 2004, there were already well over 2000 patients on ART in the Western Cape public sector, with the majority from districts other than Khayelitsha. Due to donor and research funding, many other ART projects had started, beginning in 2002. By April 2006, over 12,000 treatment-naïve adults had started ART in the provincial and city government health services, and at the time it was estimated that around half of those newly in need of treatment each year were managing to access treatment. This trajectory was followed until the end of data collection for this thesis, with corroborating data demonstrating that morbidity and mortality were constant over a number of years in the province. Increases in enrolment were therefore keeping pace

with increases in advanced HIV, but were not managing to further close the gap between treatment access and the need for treatment.

Section D: Data management and ethics

Data management and processing

Although the methods sections of each included paper give a brief account of data management, this section is intended to give a more detailed account of the data sources used in these analyses.

Khayelitsha data management

Key to the collection of data in Khayelitsha has been the use of structured clinical records, introduced in 2000 by MSF. These records, in which each visit was represented by a column on an A3 sheet, enabled excellent integration of clinical information over time, and formed the basis of the structured clinical record later used in the Province, and included by WHO as a country example in their guidelines on monitoring ART programmes.[249] Each column also serves as a source for data extraction and capture. Although it is required that data capturers interpret free-text with this system, it was felt to be the best compromise between ensuring continuity and integration of clinical care, and accurate data capture. The clinical records were adapted in 2006 throughout the province to allow more space in each column, thereby ensuring that for the majority of consultations, additional recording of clinical notes would not be necessary.

An MS Excel™ template was initially used to capture each visit from these structured records, which was soon converted to a MS Access™ database application. From mid-2002 until the end of 2004, this application (eKapa) underwent many iterations of enhancement and development and was used until the end of 2007 as the patient information system for the three original HIV clinics in Khayelitsha. A locally networked instance of the entire database was running at each clinic, with the data residing on one computer on the network. Each week the backend databases at these three clinics were synchronised with a copy held on removable storage.

The University of Cape Town (UCT) employed a full-time data quality assurance nurse from 2003 until 2006, who was responsible for verifying the quality, accuracy

and completeness of data held in the eKapa database, by systematically comparing a printed copy of the electronically held data with each source patient folder. This process was maintained for data until the end of 2005, at which point it was no longer possible to systematically verify each patient record. Database routines were then developed to highlight missing or inconsistent data, which were flagged for correction by various members of the data teams from epidemiologists working at UCT, to data quality control staff, to the MSF or government employed data capturers at the clinics.

Laboratory data were available in electronic form from late 2002, and from then until the end of 2007, electronic laboratory data, when available, were used to fill in gaps in the 6-monthly monitoring of viral load and CD4 count.

Two standard exports were built into the database application, one producing a summary table in the format of one line per patient, and one in the format of one line per visit. These exports did not include patient identifiers, and were used as the basis for the analyses of Khayelitsha ART programme data.

Western Cape data management

In late 2003, as ART availability was extending to many primary care and hospital sites in the province, a provincial committee agreed on standard structured clinical records, registers, and monthly and quarterly reports, which could be used in all facilities, irrespective of the availability of electronic systems. This end-to-end paper-based system resulted in comprehensive provincial data being collected on the limited monthly and quarterly data elements which had been defined. Based on this data, the first detailed report was produced covering until the end of March 2006, two years after the official launch of the national antiretroviral treatment programme. A year later, an updated report was produced. The first report formed the basis of one of the papers included in this thesis.

There are a number of unique features to this data collection system which enabled its success, including:

- data are reported 3 months in arrears, giving time for registers to be updated, and outcomes such as loss to follow-up and laboratory results, to be fully ascertained.
- A limited number of data elements are reported, each as an aggregate number, ensuring that they can be easily extracted from a register
- Indicators are all proportions based on the above aggregate numbers, and are very limited in number, facilitating greater completion and coverage of those that are collected

The system has been cited by WHO as a country example of appropriate cohort monitoring of ART.[249] Monthly data elements are the total number of new patients and total patients in care, reported separately for adults and children. This is sufficient for month-to-month resource planning. Quarterly indicators include, for each 6-monthly duration of follow-up and for each successive calendar quarter, mortality, loss to follow-up, viral load suppression (as a proportion < 400 copies/mL), CD4 count response (proportion with a CD4 count >=200 cells/μL in adults), and proportion on first and second-line regimens.

Those sites such as Khayelitsha which collected their data electronically, exported it in the required aggregate format for incorporation into the provincial dataset.

Household survey sampling and data management

The final data source used in this thesis was a household survey conducted in Khayelitsha in 2003/4. This survey was managed by the Infectious Disease Epidemiology Unit of the University of Cape Town. The 1996 national census was used (the 2001 census was not available at the time), to select 80 enumerator areas (areas comprising approximately 200 households) based on probability proportional to size. Aerial photographs as well as GIS data files (ArcView v3.2™) were obtained from the City of Cape Town. For formal areas, within each selected enumerator area, 10 erfs were randomly selected by the GIS software as a sample of all erfs in the given area. For informal areas, 10 spatially random points were selected by the GIS

software. Each point was then manually positioned on the accompanying aerial photograph on the nearest dwelling.

Maps of each selected enumerator area were printed from the GIS aerial photograph and street layers, with the selected erfs or households clearly indicated.

Fieldwork teams visited each enumerated household up to three times in order to interview the designated male and female adult household members. In each household, all adults aged 14-49 were enumerated. If more than one man or women in this age range lived in the household, one was randomly selected based on a procedure that utilised the given age in the enumeration table, to ensure it was repeatable.

Questionnaires were cross-checked on site by a field-work supervisor, and were double-captured into a custom MS Access™ database. The duplicate databases were compared for discrepancies, which were resolved based on the source questionnaires, prior to one of the databases being ported to Stata™ for statistical analysis.

The candidate's role in data collection and management

The candidate built and maintained the MS Access database that was used as the electronic patient information system in Khayelitsha from mid-2002 until the end of 2007, provided clinical care in the programme on a part-time basis from 2003-2005, and co-supervised the data quality assurance. The candidate co-ordinated the establishment of a Provincial structured clinical record as well as the facility-based registers and cohort monitoring system. The candidate conducted the sampling for the household survey, developed the survey database and co-supervised the survey data entry and validation.

Ethical approval

The Khayelitsha programme initially received ethical approval from the South African Medical Association. This was however superseded after the launch of the national ART programme, by ethical approval from the University of Cape Town

Research Ethics Committee (REC REF 395/2005). This approval covered all Khayelitsha analyses included in this thesis. The approval did not require individual informed consent, as it was based on the premise that all clinical care was standard of care, that the research component consisted solely of ensuring accuracy and completeness of routine data, and that data would be anonymised prior to analysis. All three of these requirements have been continuously met.

Separate approval was sought for the data linkage to the national death registry. This required the transferring of identified data to a trusted party for data matching. The Khayelitsha project received ethical approval for the linkage exercise, as did the recipient who did the linkage and returned the matched data, Mr David Bourne (REC REF 971/2008).

The household survey was also approved by the University of Cape Town Research Ethics Committee (REC REF 021/2003). The analysis of provincial data was based on routinely collected programme aggregate data, and was not submitted for ethical approval.

Chapter 2: Results in the form of published papers

Seven year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa

Paper overview

This paper presents a comprehensive set of clinical outcomes, covering temporal trends over seven years, and five years duration on ART.

The paper covers the commonly reported domains of cohort effectiveness: mortality, loss to follow-up, virological and immunological outcomes. It also covers the durability of the first-line regimen, but does not cover the tolerability of the regimen (see below). Associations with each of the main outcomes (mortality, virological failure and CD4 count response) are modelled.

Contribution to the thesis and novelty

This paper addresses the first and main objective of the thesis, as well as the question of durability in the second objective. There is currently no other study from the region that is able to report treatment outcomes over this duration or calendar period, and correct for the under-ascertainment of mortality. Other contributions of the paper that are unique to the setting are the descriptions of the immunological response conditioned on virological failure, as well as the time to meeting guideline definitions of virological failure.

Contributions of candidate

The candidate was co-responsible for the data management of the cohort since 2002, and conducted all the analyses in the manuscript. The candidate wrote and managed all drafts of the manuscript, incorporating suggestions from co-authors.

Publication status

Submitted 26 June 2009 for review to AIDS, accepted 01 October 2009.

Postscript

A further analysis was conducted subsequent to the acceptance of this paper for publication, to address the concern that patients with civil identification numbers may be different to those without. If this were the case, the weighting of patients lost to follow-up with a civil identification number to represent all patients lost to follow-up could introduce bias. The baseline CD4 counts were compared in patients with and without civil identification numbers who met the analytical loss to follow-up definition. This was restricted to those lost in the first year of ART, where the probability of mortality was highest, and differences in disease severity would be most likely to introduce bias. Although the median baseline CD4 count was slightly higher in those lost to follow-up with civil identification numbers who started ART in 2006 and 2007 (Table 1), the absolute difference was unlikely to result in large mortality differences (2006), or the numbers were too small to make valid inferences about the differences (2007).

Table 1. Comparison of baseline CD4 count in patients lost to follow-up in the first year of ART with and without civil identification numbers

	No ID number			ID number			
Year of ART	**n**	**Mean**	**Median**	**n**	**Mean**	**Median**	**p-value***
2004	29	79	76	4	71	78	0.825
2005	38	91	98	42	100	98	0.538
2006	93	99	74	87	106	95	0.063
2007	14	91	61.5	22	140	119	0.270
Total	174	93	76	155	108	97	

* rank sum test for comparison of medians

Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa

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Objectives: We report on outcomes after 7 years of a community-based antiretroviral therapy (ART) programme in Khayelitsha, South Africa, with death registry linkages to correct for mortality under-ascertainment.

Design: This is an observational cohort study.

Methods: Since inception, patient-level clinical data have been prospectively captured on-site into an electronic patient information system. Patients with available civil identification numbers who were lost to follow-up were matched with the national death registry to ascertain their vital status. Corrected mortality estimates weighted these patients to represent all patients lost to follow-up. CD4 cell count outcomes were reported conditioned on continuous virological suppression.

Results: Seven thousand, three hundred and twenty-three treatment-naive adults (68% women) started ART between 2001 and 2007, with annual enrolment increasing from 80 in 2001 to 2087 in 2006. Of 9.8% of patients lost to follow-up for at least 6 months, 32.8% had died. Corrected mortality was 20.9% at 5 years (95% confidence interval 17.9–24.3). Mortality fell over time as patients accessed care earlier (median CD4 cell count at enrolment increased from 43 cells/μl in 2001 to 131 cells/μl in 2006). Patients who remained virologically suppressed continued to gain CD4 cells at 5 years (median 22 cells/μl per 6 months). By 5 years, 14.0% of patients had failed virologically and 12.2% had been switched to second-line therapy.

Conclusion: At a time of considerable debate about future global funding of ART programmes in resource-poor settings, this study has demonstrated substantial and durable clinical benefits for those able to access ART throughout this period, in spite of increasing loss to follow-up. © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins

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Keywords: antiretroviral therapy, cohort study, death registries, HIV, loss to follow-up, resource-limited settings, South Africa

Introduction

Less than 10 years ago, opinions were divided as to the feasibility of providing antiretroviral therapy (ART) in those countries, mostly in Africa, in which the majority of people living with HIV reside [1,2]. Since then, a number of African ART programmes have demonstrated excellent adherence and clinical outcomes for the first wave of patients accessing care [3–8].

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The focus of attention is now shifting from feasibility to sustainability. Little is known about either the longer term outcomes on ART in these settings or whether the early outcomes have been sustained for patients accessing care more recently. In particular, the true outcomes of patients who are lost to follow-up are hardly known outside of study settings [7,9].

One of the first programmes that demonstrated the feasibility of ART in Southern Africa was the Khayelitsha ART programme [3], established in 2001 by Médecins Sans Frontières and the provincial government of the Western Cape, South Africa. Early outcomes from the Khayelitsha programme helped to establish the importance of a patient-centred adherence model and strong community activism for ART care [10]. This study describes outcomes for adults in Khayelitsha up to 5 years on ART and temporal trends in these outcomes over 7 years, utilizing linkages with the South African vital registration system to correct mortality estimates for increasing loss to follow-up (LTF) in recent years.

Setting

The Khayelitsha HIV treatment programme was established in 2000 at three public sector primary care clinics in Khayelitsha township, home to an estimated 500 000 people. Antenatal HIV prevalence was 22.0% in 2001 and 32.7% in 2007 [11]. ART was first provided through a pilot demonstration project in May 2001, with modest capacity to provide therapy for 180 adults [12]. By the end of 2007, the service had cumulatively enrolled over 7000 treatment-naive adults onto ART and was operating as a routine government service.

Adult patients are eligible for ART if their CD4 cell count drops below 200 cells/μl or if they have a WHO stage IV condition other than extrapulmonary tuberculosis. The initial regimen was zidovudine (ZDV) and lamivudine (3TC) together with nevirapine (NVP) or efavirenz (EFV). Stavudine (d4T) replaced ZDV in the standard first-line regimen in late 2003 in order to align with the South African national guidelines, which were implemented in April 2004 [13]. Viral load (NucliSens EasyQ HIV-1 assay; bioMérieux, Boxtel, The Netherlands) and CD4 cell count (single-platform panleucogating method) [14] testing are provided 6-monthly after starting ART. Serum alanine aminotransferase and haemoglobin are monitored for patients on NVP and ZDV, respectively. Guidelines make provision for a second-line regimen (ZDV, didanosine and lopinavir/ritonavir) to be started after virological failure is confirmed (two consecutive viral load results $\geq$5000 copies/ml, in spite of enhanced adherence promotion after the first elevated result).

The major sources of referral to the service are from acute care and tuberculosis services in the subdistrict. Nurse-based care has been central to this treatment programme since inception with more than two-thirds of consultations with nurses, and this model of care has continued to evolve over time. The frequency and intensity of clinical contact has decreased, with stable patients seen by a nurse 2 or 3-monthly, and many of the consultations for long-term stable patients being integrated into group sessions ('clubs'). The adherence model remains patient-centred but no longer includes routine home visits or a signed patient contract. Pharmacist assistants now dispense most drugs, and doctors see patients predominantly on the basis of internal referral of patients by nurses.

Prevention of mother-to-child transmission (PMTCT) services have been available since 1999, initially based on short-course ZDV [15], and since late 2003, on both short-course ZDV and peripartum NVP in women not eligible for triple therapy [16]. Data on the type of PMTCT received were not available for this analysis.

Methods

Data management and processing

Clinicians have used structured clinical records throughout the period of analysis, which are captured on-site into an electronic patient information system by dedicated data capturers. All clinical care, record keeping and data capture are part of routine patient management as per provincial guidelines. Rule-based consistency checks identify specific patients and data elements for review by quality assurance staff.

This analysis includes all data on treatment-naive patients (including those exposed only to PMTCT interventions) of age 14 years and older, until the end of 2007. Mortality and LTF estimates include patients enrolled until the middle of 2007 in order to give all patients the opportunity of meeting the LTF definition of 6 months without a clinic visit. When adjusting analyses for the year of enrolment, the first 2 years were combined into a single period due to the small numbers enrolled in these years and similarity in patient profile.

Civil identification numbers, where available, were cross-checked in the national death registry to confirm or ascertain dates of death for those with registered deaths. It was not possible to differentiate deaths due to HIV from deaths due to other causes. All data were anonymized prior to being made available for analysis.

Follow-up laboratory results were considered as representing the nearest 6-monthly follow-up duration. Baseline CD4 cell counts included measures from

12 months prior to 1-week posttreatment initiation. If more than one measure was available, the measure closest to baseline or 6-monthly duration was used. When comparing viral loads on first and second-line regimens, first-line viral loads were restricted to tests done prior to the switching. Second-line viral loads were restricted to measures that followed the initiation of second-line by at least 3 months in order to exclude repeated baseline viral loads at the initiation of second-line. Laboratory outcomes are presented only for those patients on treatment in whom test results were available, and no assumption is made on laboratory outcomes in those who missed a scheduled test or who were lost to care at the time.

Analysis

Kaplan–Meier estimates of time to death and LTF (date last seen) are described. A weighted Kaplan–Meier approach was used to correct the mortality estimate for those who were LTF but had died, by weighting those patients who were LTF but for whom a definitive outcome could be established from the death registry, to represent all patients lost to follow-up [17]. Weights were calculated separately by year and duration of follow-up. Bootstrap confidence intervals (CIs) for the weighted Kaplan–Meier failure estimates were calculated by sampling from the dataset with replacement 1000 times. Patients who were known to have transferred to other services were right censored at the date of transfer. Cox proportional hazard models based on the same weighted data were used to explore associations with early (<3 months) and late mortality.

Virological responses were described as the proportion below 400 copies/ml at each year of follow-up for all patients, and separately for patients on first and second-line regimens. Virological responses on first and second-line therapy were compared across all durations in a logistic regression model clustered on individuals with robust standard errors. CD4 cell responses were described as median absolute value, change from baseline count and change from previous count at each duration of follow-up. This was repeated on a subset of patients who had been continuously virologically suppressed until the CD4 cell count measure. Proportions were compared using the chi-squared test and medians using the rank sum test.

Time to confirmed virological failure and time to the initiation of second-line therapy were described as standard Kaplan–Meier estimates, and associations with virological failure were explored with a standard Cox model. A population-averaged linear regression model with an exchangeable correlation matrix was used to explore associations with CD4 cell count responses in each 6-month interval, limited to patients with continuous virological suppression.

All analyses were conducted using Stata statistical software, version 10.0 (Stata-Corp Inc., College Station, Texas, USA). The analysis of routine cohort data and the linkage to the national death registry were both approved by the University of Cape Town Research Ethics Committee.

Results

Annual enrolment increased from 80 treatment-naive adult patients in 2001 to 2087 in 2006 (Table 1), with a total of 7323 enrolled during the period under analysis. Women constituted 68.2% of the cohort and were younger at enrolment than men (median 31 vs. 36 years, $P < 0.001$). Overall, 3.7% of women initiated ART while pregnant and 11.1% had previously received PMTCT interventions. Median baseline CD4 cell count increased from 43 [interquartile range (IQR) 13–95] cells/μl in 2001/2002 to 131 (IQR 64–191) cells/μl in 2007. The proportion with clinically advanced disease (AIDS as defined by WHO clinical stage IV) [18,19] decreased over the same period from 54.5 to 28.9%. The proportion initiating ART while already on treatment for tuberculosis increased from 22.7 to 42.4%.

Civil identification numbers were available for 57.0% of all patients and 70.6% of patients enrolled in 2007 (Webtable 1). Cross-sectionally, 9.8% of patients enrolled by the middle of 2007 (628/6402) had been LTF. Just under half of those LTF had a civil identification number (46.7%), of whom 32.8% had a registered death before the end of 2007. Patients lost in their first year of treatment (59.2%) were more likely to have died compared with those lost thereafter (42.4 vs. 18.1%, $P < 0.001$).

In patients whose deaths were reported to the services and for whom a civil identification number was available, 90.5% (172/190) were matched in the death registry, whereas 99.9% (2941/2944) of patients known to be alive and with valid civil identification numbers were not found in the registry, reflecting the sensitivity and specificity of the data linkage.

The cumulative estimate of mortality based on clinic-held data was 15.5% (95% CI 13.1–18.3) at 5 years (Fig. 1a), whereas the equivalent estimate of LTF was 23.4% (95% CI 20.5–26.6). Combining LTF and mortality, 35.3% (95% CI 32.1–38.6) of patients were lost to care at 5 years. LTF has occurred earlier with each successive year of enrolment (Fig. 1b). The weighted estimates of mortality, including patients LTF who could be matched in the death registry, were 9.9% (95% CI 8.9–10.9), 12.6% (95% CI 11.5–13.8) and 20.9% (95% CI 17.9–24.3) at 1, 2 and 5 years, respectively (Fig. 1c). Incorporating the linkage data, overall mortality has decreased over time (Fig. 1d).

Low baseline CD4 cell count, an AIDS diagnosis and a low body weight were all strongly associated with

Table 1. Baseline characteristics of adult patients starting antiretroviral therapy in Khayelitsha: 2001–2007.

Year of starting ART	2001/2002	2003	2004	2005	2006	2007	Combined
Patients enrolled							
n	286	388	1061	1641	2087	1860	7323
Sex, *n* (%)							
Male	85 (29.7)	121 (31.2)	317 (29.9)	492 (30.0)	734 (35.2)	613 (33.0)	2362 (32.3)
Age (years)							
Women, median (IQR)	31 (26–36)	30 (27–34)	31 (27–37)	31 (27–36)	31 (27–38)	31 (27–37)	31 (27–37)
Men, median (IQR)	35 (30–39)	36 (30–41)	36 (31–41)	36 (31–42)	36 (31–42)	37 (32–42)	36 (31–42)
Baseline CD4 cell count (cells/μl)							
Tested (*n*, %)	284 (99.3)	383 (98.7)	1051 (99.1)	1565 (95.4)	1894 (90.8)	1428 (76.8)	6605 (90.2)
Median (IQR)	42.5 (13–95)	72 (22–126)	85 (37–141)	100 (44–157)	109 (52–169)	131 (64–191)	101 (45–164)
Baseline viral load (copies/ml)							
Tested (*n*, %)	271 (94.8)	263 (67.8)	927 (87.4)	1481 (90.2)	519 (24.9)	26 (1.4)	3487 (47.6)
Log_{10} median (IQR)	5.1 (4.7–5.6)	5.2 (4.6–5.6)	5.2 (4.7–5.7)	5.0 (4.5–5.5)	5.0 (4.5–5.6)	4.6 (4.0–5.4)	5.1 (4.6–5.6)
WHO stage, *n* (%)							
I/II	2 (0.7)	6 (1.5)	102 (9.6)	240 (14.6)	374 (17.9)	428 (23.0)	1152 (15.7)
III	128 (44.8)	183 (47.2)	514 (48.4)	791 (48.2)	1062 (50.9)	893 (48.0)	3571 (48.8)
IV	156 (54.5)	199 (51.3)	445 (41.9)	610 (37.2)	651 (31.2)	538 (28.9)	2599 (35.5)
Weight (kg)							
Tested (*n*, %)	285 (99.7)	379 (97.7)	1026 (96.7)	1563 (95.2)	2037 (97.6)	1532 (82.4)	6822 (93.2)
Median (IQR)	56.8 (50.0–65.0)	59 (50.0–68.0)	59 (52.0–66.5)	58 (51.5–66.5)	59.3 (52.0–67.2)	60 (52.2–68.0)	59 (51.6–67.0)
Tuberculosis							
n (%)	65 (22.7)	105 (27.1)	316 (29.8)	618 (37.7)	867 (41.5)	789 (42.4)	2760 (37.7)
Pregnant							
n (% of women)	1 (0.5)	3 (1.1)	14 (1.9)	53 (4.6)	38 (2.8)	75 (6.0)	184 (3.7)
PMTCT exposed							
n (% of women)	26 (12.9)	47 (17.6)	108 (14.5)	163 (14.2)	119 (8.8)	88 (7.1)	551 (11.1)
Baseline regimen, *n* (%)							
ZDV/3TC/EFV	170 (59.4)	247 (63.7)	6 (0.6)	32 (2.0)	93 (4.5)	94 (5.1)	642 (8.8)
ZDV/3TC/NVP	108 (37.8)	17 (4.4)	16 (1.5)	63 (3.8)	150 (7.2)	258 (13.9)	612 (8.4)
D4T/3TC/EFV	2 (0.7)	106 (27.3)	279 (26.3)	859 (52.3)	1058 (50.7)	887 (47.7)	3191 (43.6)
D4T/3TC/NVP	2 (0.7)	17 (4.4)	759 (71.5)	687 (41.9)	774 (37.1)	579 (31.1)	2818 (38.5)
Other	4 (1.4)	1 (0.3)	1 (0.1)	0 (0.0)	12 (0.6)	42 (2.3)	60 (0.8)

3TC, lamivudine; ART, antiretroviral therapy; D4T, stavudine; EFV, efavirenz; IQR, interquartile range; NVP, nevirapine; ZDV, zidovudine.

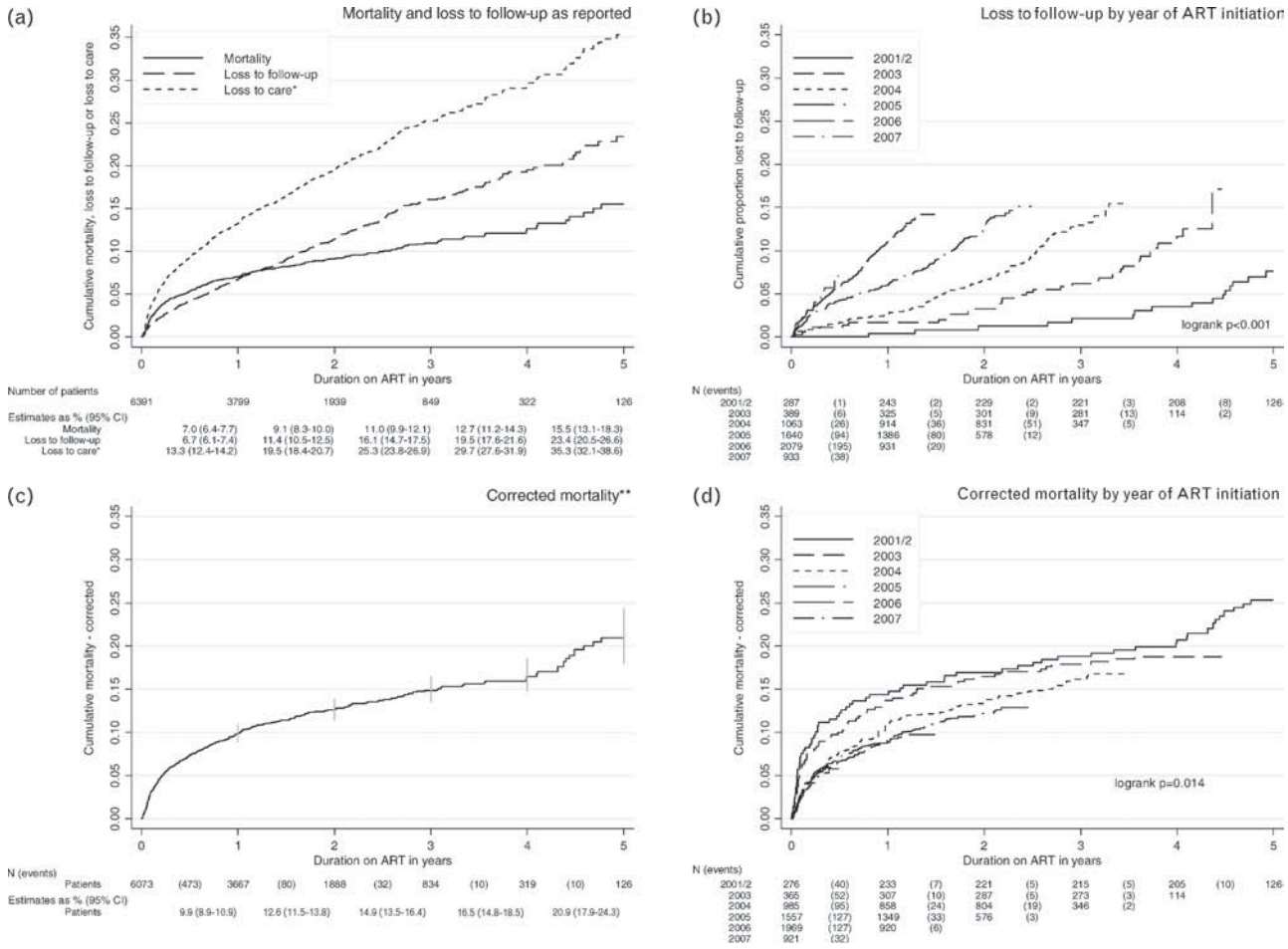

Fig. 1. Cumulative estimates of mortality, loss to follow-up and loss to care. Kaplan–Meier estimates of reported mortality and loss to follow-up (a), loss to follow-up by year of initiation (b), corrected mortality (c) and corrected mortality by year of initiation (d). ART, antiretroviral therapy; CI, confidence interval. *Loss to care includes both those who have died and those lost to follow-up. **Vital status was ascertained for patients lost to follow-up from the national death registry if a civil identification number was available. These patients were weighted in this analysis to represent all patients lost to follow-up. Vertical bars represent 95% CIs.

mortality in the first 3 months on ART (Table 2) and remained associated, although attenuated, beyond 3 months. Older age (>50 years) was associated with higher mortality after 3 months on ART. Year of ART initiation was not associated with mortality after adjustment for baseline characteristics.

For all patients combined, 87.6, 88.1 and 83.8% of those who remained in care and received viral load tests were virologically suppressed (<400 copies/ml) at 1, 3 and 5 years, respectively (Table 3). Patients on second-line ART were less likely to be virologically suppressed compared with patients remaining on first line at equivalent durations on ART [odds ratio (OR) 0.51, 95% CI 0.26–1.01], although 22 out of 29 (75.9%) patients on second-line ART at 5 years were virologically suppressed.

Patients who remained virologically suppressed throughout follow-up had gained a median of 474 (IQR 341–660) CD4 cells/μl by 5 years and continued to gain a median of 22 cells/μl per 6-month period between 4 and 5 years on ART (Table 3). Additional factors independently associated with CD4 cell count gain (Table 4) were female sex, younger age and measures of disease advancement at ART initiation (AIDS, tuberculosis and low CD4 cell count). At 5 years on ART, 3.7, 11.9 and 25.7% of virologically suppressed patients had CD4 count values less than 200, 200–349 and 350–499 cells/μl, respectively.

By 5 years, 14.0% (95% CI 11.9–16.4) of patients had met the guideline definition of confirmed virological failure (Fig. 2) and 12.2% (95% CI 10.1–14.8) had started second-line therapy. Seventy-four percent of those starting second-line therapy formally met the guideline definition and started second line a median 5.3 (IQR 2.2–11.2) months after the date of the second raised viral load. The remaining patients were started on second-line therapy with one of the raised values being between 400 and 5000 copies/ml or without a confirmatory viral load test.

Table 2. Characteristics at the start of antiretroviral treatment associated with mortality in multivariate weighted Cox proportional hazard models.

	First 3 months on ART[a]			Beyond 3 months on ART[b]		
	AHR	95% CI	*P*	AHR	95% CI	*P*
Age ≥50 years	1.2	0.7–2.3	0.523	2.3	1.4–3.6	<0.001
Male sex	1.2	0.9–1.6	0.160	1.3	1.0–1.7	0.071
CD4 cell count category (cells/μl)			<0.001			0.003
0–50	3.9	2.3–6.6		1.8	1.2–2.6	
50–149	1.9	1.2–3.3		1.2	0.8–1.7	
150–249 (ref.)	1.0	–		1.0	–	
AIDS diagnosis when starting ART	1.8	1.3–2.4	<0.001	1.4	1.0–1.9	0.038
Baseline weight (per 10 kg)	0.6	0.5–0.6	<0.001	0.8	0.7–0.9	<0.001
Was on TB treatment when starting ART	1.1	0.8–1.4	0.509	0.7	0.5–1.0	0.071
Year of starting ART			0.275			0.941
2001/2002	1.3	0.7–2.5		1.2	0.3–5.1	
2003	1.2	0.6–2.1		1.2	0.3–5.5	
2004	0.7	0.4–1.3		1.4	0.3–6.2	
2005	1.0	0.6–1.7		1.2	0.3–5.0	
2006	1.0	0.6–1.7		1.1	0.3–4.7	
2007 (ref.)	1.0	–		1.0	–	

AHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; TB, tuberculosis.
[a]5346 observations, weighted $n = 5631$.
[b]4833 observations, weighted $n = 4931$.

ART interruptions, PMTCT exposure, low initial CD4 cell count and the use of NVP (especially concomitantly with treatment for tuberculosis) were all independently associated with virological failure (Table 5).

Discussion

Our analysis demonstrates that ART benefits, in a poorly resourced primary care setting, are durable, with almost

Table 3. Viral load and CD4 cell count responses for up to 5 years on antiretroviral therapy.

	1 year	2 years	3 years	4 years	5 years
Viral load					
Combined					
Total in care	4512	2561	1235	458	191
Tested (%)	3932 (87.1)	2198 (85.8)	983 (79.6)	351 (76.6)	148 (77.5)
Suppressed (%) [<400 copies/ml]	3446 (87.6)	1905 (86.7)	866 (88.1)	311 (88.6)	124 (83.8)
First line					
Total in care (%)	4505 (99.8)	2506 (97.9)	1147 (92.9)	405 (88.4)	155 (81.2)
Tested (%)	3890 (86.3)	2127 (84.9)	914 (79.7)	310 (76.5)	119 (76.8)
Suppressed (%) [<400 copies/ml]	3407 (87.6)	1851 (87.0)	812 (88.8)	282 (91.0)	102 (85.7)
Second line					
Total in care (%)	7 (0.2)	55 (2.1)	88 (7.1)	53 (11.6)	36 (18.8)
Tested (%)	5 (71.4)	47 (85.5)	63 (71.6)	41 (77.4)	29 (80.6)
Suppressed (%) [<400 copies/ml]	4 (80.0)	31 (66.0)	50 (79.4)	29 (70.7)	22 (75.9)
CD4 cell count					
All patients					
Total in care	4512	2561	1235	458	191
Tests available	3823	2108	931	341	127
CD4 cell count, median, cells/μl (IQR)	297 (209–397)	383 (276–515)	425.5 (309.5–581)	486 (346.5–669)	512 (353–689)
Change from baseline, median (IQR)	192 (116–282)	282 (180–406)	341 (224–488)	413 (263–580)	442 (266–615)
Change over 6 months, median (IQR)	51 (−7 to 111)	43 (−18 to 111)	24.5 (−55 to 99.5)	20.5 (−54.5 to 124.5)	6 (−85 to 116)
Patients with continuous viral load suppression documented					
Tests available	3380	1847	820	307	109
CD4 cell count, median, cells/μl (IQR)	304 (218–404)	398 (299–531)	459.5 (341.5–601)	511 (391–714)	542 (393–725)
Change from baseline, median (IQR)	198 (124–288)	300 (203–420)	371 (251–509)	441 (317–629)	474 (340.5–659.5)
Change over 6 months, median (IQR)	55 (2–116)	49 (−11 to 117)	34 (−44 to 105)	32.5 (−51 to 141)	22 (−78 to 147)

IQR, interquartile range.

Table 4. Multivariate associations with 6-monthly CD4 cell count changes.

	CD4 cell count changes[a] over 6 months		
	Coefficient[b]	95% CI	*P*
Male sex	−14.3	−17.1 to −11.5	<0.001
AIDS diagnosis at the start of ART	3.0	0.4–5.7	0.026
Had TB at the start of ART	4.7	1.8–7.6	0.002
Age at the start of ART (years)			0.107
16–24 (ref)	0.0	–	
25–49	−4.5	−9.1 to 0.1	
≥50	−7.4	−15.4 to 0.6	
CD4 cell count at the start of ART (cells/μl)			<0.001
0–50	13.2	9.7–16.7	
50–149	2.2	−1.1 to 5.5	
150–249 (ref.)	0.0	–	
Duration of ART (months)			<0.001
6	122.7	117.6–127.9	
12–30	25.2	20.5–29.9	
≥30 (ref.)	0.0		
Constant	33.7	27.6–39.7	

ART, antiretroviral therapy; CI, confidence interval; TB, tuberculosis.
[a]CD4 cell count changes are change for each 6-monthly interval in patients who continuously had viral loads below 400 copies/ml up until the time of the second CD4 cell count measurement. Population-averaged linear regression model with an exchangeable correlation matrix, clustered on individual patient. Thirteen thousand and forty-five observations are reported in 4314 patients.
[b]Adjusted for other variables.

80% of patients remaining alive at 5 years, of whom more than 80% of those tested were virologically suppressed. Improvements in CD4 cell count and clinical stage at ART initiation were translated in absolute terms into improved survival since 2004. After adjustment for these measures, we found that the rapid scale-up in patient numbers has not resulted in increased mortality. Although the link between improved access to care and reduced early mortality has been previously reported in the broader provincial programme of which the Khayelitsha cohort is a part [7], the current analysis was able to correct for possible underascertainment of mortality.

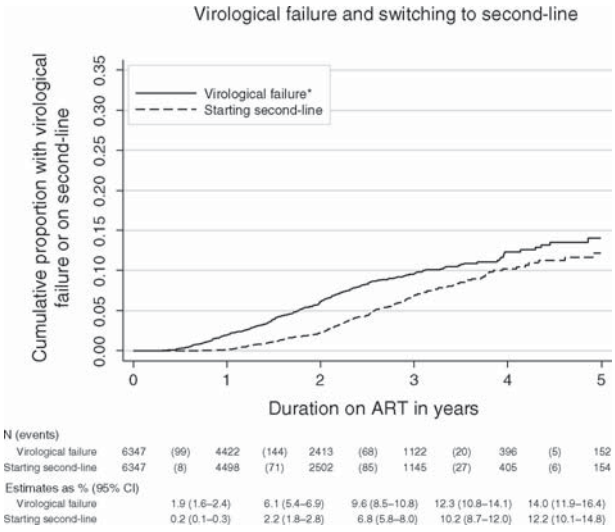

Fig. 2. Time to virological failure and starting second-line therapy. *Virological failure defined as two consecutive viral loads above 5000 copies/ml, at the time of the second elevated value. ART, antiretroviral therapy; CI, confidence interval.

The relatively high proportion of patients who have remained virologically suppressed for up to 5 years on treatment is reassuring. Nevertheless, almost one in five patients reaching 5 years are on a second-line regimen in spite of the delays in switching to second line, suggesting that a substantial number of patients are going to need to access second-line therapy as programmes mature. Predictors of both virological failure and CD4 cell count gain conditioned on continuous virological suppression are rarely reported from scale-up settings. The association between virological failure and PMTCT exposure, in spite of the likely misclassification of some non-NVP exposures, adds to concerns that NVP-based PMTCT may compromise future ART effectiveness [20,21]. The 1.6-fold increased risk of virological failure following each treatment interruption is also of concern, especially given the high proportion of patients who develop serious toxicity on the current first-line regimens in use, which often necessitates treatment interruption [22], and that the majority of interruptions in patients lost to follow-up will not be staggered to cover the longer half-life of non-nucleoside reverse transcriptase inhibitors (NNRTIs) [23,24].

Patients in this cohort who remained virologically suppressed continued to restore CD4 cells throughout follow-up, with the rate of increase slowing as CD4 cell counts reached the normal range. This finding is similar to the equivalent subgroups of patients in recent analyses of European and North American cohorts [25,26] but differs from a collaborative analysis from resource-limited

Table 5. Multivariate associations with confirmed virological failure.

	Virological failure[a]		
	AHR	95% CI	*P*
Male sex	1.0	0.8–1.3	0.977
Exposed to PMTCT prior to ART	1.5	1.1–2.0	0.024
Interruptions to ART (per interruption ≥7 days)	1.6	1.1–2.2	0.012
Age at the start of ART (years)			<0.001
16–24	2.0	1.5–2.7	
25–49 (ref.)	1.0	–	
≥50	0.9	0.5–1.7	
CD4 cell count at the start of ART (cells/μl)			0.009
0–50	1.7	1.2–2.3	
50–149	1.4	1.0–1.9	
150–249 (ref.)	1.0	–	
NNRTI used and TB status at the start of ART			0.002
EFV, no TB (ref.)	1.0	–	
EFV, TB	1.3	0.9–1.9	
NVP, no TB	1.5	1.1–2.1	
NVP, TB	2.5	1.6–4.1	
Year of ART initiation			<0.001
2001/2002	2.1	1.4–3.0	
2003	1.3	0.8–2.0	
2004	0.9	0.7–1.3	
2005 (ref)	1.0	–	
2006	1.1	0.8–1.6	
2007	0.7	0.2–1.8	

AHR, adjusted hazard ratio; ART, antiretroviral therapy; CI, confidence interval; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PMTCT, prevention of mother-to-child transmission of HIV; TB, tuberculosis.
[a]Virological failure defined as two consecutive viral loads of at least 5000 copies/ml; $n = 5743$, Cox proportional hazards model.

settings, which was not conditioned on viral load suppression [27]. The negative associations between CD4 cell count response and older age and male sex have also previously been described [27]. In total, after 5 years, 41.3% of virologically suppressed patients had a CD4 cell count below 500 cells/μl compared with 35.8% in a comparable study in Switzerland [28]. This difference is most likely the result of the lower baseline CD4 cell counts of patients in Khayelitsha and highlights how advanced disease at enrolment results in more time spent in CD4 cell count strata that carry substantial morbidity and mortality [29].

It is well established that immunological measures are poorly predictive of virological failure [30–33]. In spite of the controversies around the utility of viral load monitoring in this setting [34,35], there is extensive pressure for the more widespread availability of viral load monitoring [36]. The current study is one of the very few in southern Africa to report on the systematic use of viral load testing to identify treatment failure. Applied in a context of rapid scale-up, the South African guidelines still result in an average delay of many months between the first evidence of failure and subsequent switching. This is the result of the time taken to confirm the failure, the pressures on service providers due to increasing patient numbers and a reluctance on the part of clinicians to commit patients to second-line therapy before adherence issues have been exhaustively addressed.

It is unknown whether the delays in switching therapy in viraemic patients as described in our study compromise the effectiveness of subsequent regimens or whether there would be additional consequences of leaving patients on their first-line regimen until they fail immunologically. Two recent African studies [37,38] reported genotypic resistance data at the time of failure of first-line ART. As expected, both studies reported widespread resistance to 3TC and NNRTIs. The Malawian study, in which viral load monitoring is not available, reported a high prevalence of thymidine analogue mutations and the K65R mutation, but the South African study, in which viral load monitoring is available, reported a much lower prevalence of these mutations, suggesting that virological monitoring will better preserve future treatment options. With increasing numbers of patients on second-line regimens, however, some of whom are already failing second line, pressure for a third-line regimen in resource-limited settings is emerging and there is more concern from clinicians about switching too late than too early.

Many of those who have failed virologically and switched to second-line therapy may have had suboptimal adherence to their first-line regimens and may be less adherent than those who have remained on first line. This, in addition to the higher pill burden and more complex dosing intervals of the available second-line regimen, could explain the lower proportion of patients

on second-line therapy who were virologically suppressed at each duration of follow-up.

Our finding that LTF is increasing with calendar time is in line with previous studies from resource-limited settings [7,39], which we ascribe to rapidly increasing patient numbers and resultant pressure under which services are operating, and the declining ability of services to actively trace patients who miss appointments.

A number of tracing studies [40–42] done in southern Africa have demonstrated that upwards of a quarter of patients LTF have died. Our analysis confirms high mortality in those lost to follow-up (33%). We also found that the probability of death amongst those LTF is related to the duration on ART prior to being lost. In order to understand the long-term effectiveness of ART in southern Africa, it will be necessary to establish well supported sentinel cohorts in which ascertainment of both laboratory and vital status outcomes is prioritized.

Initial positive reports of patient outcomes on ART in resource-poor settings were interpreted by many as demonstration projects, made possible by the investment of additional resources that might not be sustained over time and when scaled up. Khayelitsha is, however, one of the most difficult areas in the Western Cape Province in which to provide health services due to chronic under-resourcing and an enormous burden of infectious and noncommunicable disease. The Khayelitsha ART service has been predominantly staffed and run by government health services for the past few years and has faced the same stresses, understaffing and crises faced by the health services in the area in general. When compared with routine reporting across the entire province [7], or other cohort studies in the province [43], Khayelitsha is an averagely performing subdistrict. It is, thus, likely that our findings are generalizable to other low and middle-income countries, but aspects may not apply to programmes without virological monitoring. In the first group of patients accessing ART in Botswana followed up to 5 years [8], cumulative mortality and LTF at 5 years were 21.8 and 21.0% compared with 15.5 and 23.4% in our study prior to incorporating death registry data. Available viral load suppression measures in the Botswana study were comparable or higher than in our study at each duration on ART. In a Senegalese cohort, cumulative mortality at 5 years was 24.6% in a cohort with very low reported LTF [44].

This study has a number of limitations. First, although the level of ascertainment of deaths through data-linkage with national vital statistics may be an improvement on what is feasible in many parts of southern Africa, the sensitivity of the record-linkage was only 90%, indicating residual underascertainment of a small proportion of deaths. Although we do not consider that there is any systematic bias introduced by patients who do and do not have recorded civil identification numbers, the lower availability of this linkage field for patients starting ART in the first few years of the cohort could have introduced a bias. Second, laboratory outcomes are limited to measures that were available, and patients without tests available or who were alive but no longer in care might have altered these findings had it been possible to test them. The lack of detailed exposure data impeded some of the explorations such as the association between PMTCT interventions and subsequent virological failure on HAART, in which the inclusion of NVP in the PMTCT intervention was not known. Finally, the absence of resistance data in patients who were failing virologically limited our ability to explore the effect of delays in switching therapy on future treatment options.

At a time when there is uncertainty about continued and increased direct bilateral and multilateral funding of ART-specific interventions in countries with limited resources, these findings provide considerable reassurance that the benefits of ART in these settings are sustained. Many of the early innovations to support patient adherence have endured the rapid scale-up in patient enrolment and are today standard of care in Khayelitsha and beyond. The scale-up has itself led to further health service developments such as task shifting to nurse-managed clinical care. This study has demonstrated substantial and durable clinical benefits for those able to access the intervention throughout a 7-year period.

Acknowledgements

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Webtable 1. Linkages to the death register in patients lost to follow-up.

	≤2004	2005	2006	2007	Total
Patients starting ART by mid-2007					
n	1735	1641	2087	939	6402
Patients with valid recorded civil identification numbers					
n (% of total)	689 (39.7%)	966 (58.9%)	1332 (63.8%)	663 (70.6%)	3650 (57.0%)
Patients lost to follow-up					
Lost in first year on ART - n (% of total lost)	33 (19.3%)	92 (48.9%)	204 (90.7%)	43 (100%)	372 (59.2%)
Lost between 1 and 5 years on ART - n (% of total lost)	138 (80.7%)	96 (51.1%)	21 (9.3%)	0 (0.0%)	256 (40.8%)
Total lost - n (% of total started)	171 (9.9%)	188 (11.5%)	225 (10.8%)	43 (4.6%)	628 (9.8%)
Patients lost to follow-up with civil ID numbers					
Lost in first year on ART - n (% of lost)	4 (12.1%)	48 (52.2%)	97 (47.5%)	28 (65.1%)	177 (47.6%)
Lost between 1 and 5 years on ART - n (% of lost)	51 (37.0%)	55 (57.3%)	9 (42.9%)	0	116 (45.3%)
Total - n (% of lost)	55 (32.2%)	103 (54.8%)	106 (47.1%)	28 (65.1%)	293 (46.7%)
Weights used in the corrected mortality estimates					
For patients lost in first year on ART	8.3	1.9	2.1	1.5	
For patients lost from 1 to 3 years	2.9	1.7	2.3		
For patients lost from 3 to 5 years	1.9				
Deaths in patients lost to follow-up with ID numbers					
Lost in first year on ART - n (% of lost)	3 (75.0%)	19 (39.6%)	38 (39.2%)	15 (53.6%)	75 (42.4%)
Lost between 1 and 5 years on ART -n (% of lost)	6 (11.8%)	13 (23.6%)	1 (11.1%)	0	21 (18.1%)
Total - n (% of lost)	9 (16.4%)	32 (31.1%)	39 (36.8%)	15 (53.6%)	96 (32.8%)

ART, antiretroviral therapy; ID, identification.

Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort

Paper overview

This analysis, combines data from two cohorts in the Western Cape Province, and examines the time to the first substitution due to toxicity in patients on the commonly prescribed first-line antiretroviral drugs in this setting.

Contribution to the thesis and novelty

This paper addresses the tolerability question in the second objective of the thesis. Accurate data on the reasons for regimen changes are rarely available in the region, and this paper is one of very few to comprehensively describe treatment-limiting toxicities across all the commonly used first-line agents. The analysis was also able to identify and for the first time quantify the excess risk for symptomatic hyperlactataemia or lactic acidosis in overweight women starting ART on d4T.

Contributions of candidate

These data were first presented by the candidate based just on the Khayelitsha data at the Conference on Retroviruses and Opportunistic Infections in 2006. The subsequent addition of data from the Gugulethu cohort (950/2679 patients) enabled longer term toxicities on d4T to be described as it had been more commonly used in this cohort than in Khayelitsha in 2002 and 2003. The candidate was responsible for the data processing and combining the data from both cohorts, and for all analyses. The candidate was primarily responsible for drafting all versions of the manuscript, which included integrating comments from co-authors.

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Substitutions due to antiretroviral toxicity or contraindication in the first 3 years of antiretroviral therapy in a large South African cohort

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Introduction: The patterns and reasons for antiretroviral therapy (ART) drug substitutions are poorly described in resource-limited settings.
Methods: Time to and reason for drug substitution were recorded in treatment-naive adults receiving ART in two primary care treatment programmes in Cape Town. The cumulative proportion of patients having therapy changed because of toxicity was described for each drug, and associations with these changes were explored in multivariate models.
Results: Analysis included 2,679 individuals followed for a median of 11 months. Median CD4$^+$ T-cell count at baseline was 85 cells/μl. Mean weight was 59 kg, mean age was 32 years and 71% were women. All started non-nucleoside reverse transcriptase inhibitor-based ART (60% on efavrienz) and 75% started on stavudine (d4T). After 3 years, 75% remained in care on-site, of whom 72% remained on their initial regimen. Substitutions due to toxicity of nevirapine (8% by 3 years), efavirenz (2%) and zidovudine (8%) occurred early. Substitutions on d4T occurred in 21% of patients by 3 years, due to symptomatic hyperlactataemia (5%), lipodystrophy (9%) or peripheral neuropathy (6%), and continued to accumulate over time. Those at greatest risk of hyperlactataemia or lipodystrophy were women on ART ≥6 months, weighing ≥75 kg at baseline.
Discussion: A high proportion of adult patients are able to tolerate their initial ART regimen for up to 3 years. In most instances treatment-limiting toxicities occur early, but continue to accumulate over time in patients on d4T. Whilst awaiting other treatment options, the risks of known toxicities could be minimized through early identification of patients at the highest risk.

Introduction

With the dramatic scaling up of antiretroviral therapy (ART) in South Africa and other resource-limited settings, there has been a move towards highly standardized treatment approaches [1,2]. As in many countries, the South African national ART programme is based on the World Health Organization (WHO) guidelines, with provision for two treatment regimens: an initial non-nucleoside reverse transcriptase enzyme inhibitor (NNRTI)-based regimen followed by a protease inhibitor (PI)-based regimen [2]. Only seven antiretrovirals are routinely available for treatment in South Africa; the limited treatment options here and in other resource-poor settings makes the changing of regimens, because of virological failure, contraindications or drug toxicity, a particularly important issue in the scale up of national HIV treatment programmes.

One of the most frequently used nucleoside reverse transcriptase inhibitors (NRTIs) in the first-line regimen in South Africa is stavudine (d4T), which is increasingly recognized as contributing to a number of

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toxicities such as peripheral neuropathy, lipodystrophic body changes and hyperlactataemia. These may significantly effect the well-being and adherence of individuals on first-line therapy, as well as the ability of programmes to simplify clinical interventions [3–7].

There are, however, few reliable estimates of the incidence of toxicities of commonly used antiretrovirals in resource-poor settings. Existing insights come primarily from clinical trials and research populations in Europe and North America, where the thresholds for modifying therapy are likely to be much lower than in contexts with more limited choices of antiretrovirals. In large scale-up settings accurately determining the incidence of toxicities is a major challenge because of service and information system constraints. In these settings the reporting of those toxicities that result in a drug change is an approach that is frequently recommended [8]. The aim of this study was to describe the contribution of individual drugs to toxicity- or contraindication-based modification of ART in a large public sector treatment cohort in South Africa.

Methods

Data were drawn from ART services in two districts in Cape Town, Nyanga and Khayelitsha. The estimated combined population in these districts is 700,000; both communities are densely populated and predominantly poor, with unemployment over 40%, and a high burden of HIV (2005 antenatal HIV seroprevalence approximately 30%) [9–11]. Tuberculosis case finding is extremely high in both districts (>1,000/100,000).

ART has been offered since 2001 in Khayelitsha and 2002 in Nyanga. There are three clinics in Khayelitsha and one in Nyanga providing ART. By August 2006 ART was being provided free of charge to 5,390 people attending the four antiretroviral clinics in these districts. Specimens for laboratory testing are processed on-site or are transported the same day to a single regional laboratory, and point-of-care lactate testing (Accutrend™, Roche Diagnostics, Randburg, South Africa) has been available at the clinics since early 2005. Each site maintains electronic information systems to capture routine clinical information from patient records. The University of Cape Town Research Ethics Committee has provided approval for the data collection and analysis in both districts.

Treatment regimens and clinical protocols

At all sites, treatment was provided according to the South African National ART guidelines [2,12]. In the first 2 years of the Khayelitsha programme (2001–2003), however, zidovudine (AZT) replaced d4T in the initial NRTI backbone. Patients were reviewed at least monthly until their third month on ART, after which they had a scheduled clinical visit at least every 3 or 4 months. Care was provided by either doctors or professional nurses with HIV clinical training, with all sites having a doctor permanently available. $CD4^+$ T-cell counts and viral loads were done at baseline and then 4 or 6 monthly thereafter. Safety blood tests were provided according to standard protocols – monthly haemoglobin tests in patients on AZT and monthly alanine transferase (ALT) tests in patients on nevirapine (NVP) for the first 3 months, at 6 months, and then 6 monthly.

Single drug changes were defined as *substitutions*. These included changes due to a drug-related adverse event or toxicity (for example, AZT-induced anaemia or NVP hypersensitivity) as well as changes due to potential drug interactions or contraindications (for example, avoiding EFV in pregnancy or NVP with concomitant anti-tuberculosis therapy). Although previous studies have described that relatively few of the deaths in these programmes can be ascribed to antiretroviral toxicities [13,14], if a patient death was related to toxicity of a drug which was not discontinued prior to death, a drug discontinuation due to toxicity was recorded. Changes of two or more drugs due to virological failure were described as a *switch* in therapy. Rates of virological failure in this cohort have been described previously [15,16].

Protocols in use by clinicians recommended that adverse drug reactions were graded using the AIDS Clinical Trial Group (ACTG) toxicity scale [17], with indications for toxicity-related substitutions being grade 3 or 4 toxicities. The working definition of symptomatic hyperlactataemia applied in this setting was an uncuffed venous lactate in excess of 2.5 mmol/l in a symptomatic patient with no signs of acidosis. For this analysis, patients with symptomatic hyperlactataemia or lactic acidosis were combined into a single group (SHLA).

Analysis

All patients initiating ART from programme commencement until August 2005 (Nyanga) or December 2004 (Khayelitsha) were considered for analysis, and patients were followed until August 2005 and June 2005, respectively. Those who were treatment-experienced at presentation and children <14 years old were excluded. Patient time on each starting antiretroviral drug was included from treatment commencement until the substitution of that drug, with patients being right-censored at either their last visit prior to the cut-off date, or at the date of discontinuing therapy for other reasons such as death and loss to follow up. The reasons for drug substitutions were coded according to the reasons recorded by clinicians in the clinical records.

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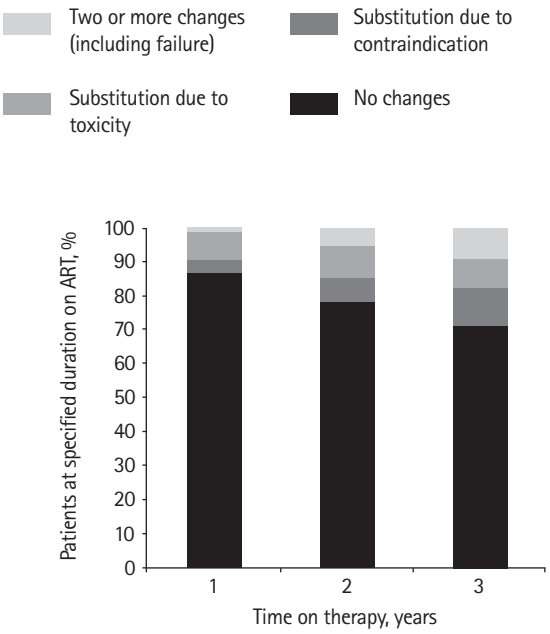
Table 1. Characteristics of patients included in the analysis

Characteristic	Baseline value
Total and setting	
Total participants	2,679
Khayelitsha	1,729 (65)
Nyanga	950 (35)
Gender	
Male	783 (29)
Age on starting ART, years	32 (28–38)
Baseline CD4$^+$ T-cell count, cells/μl	83 (34–140)
Baseline viral load, $\log_{10}$ copies	5.5 (4.6–5.5)
WHO clinical stage on starting ART	
Stage 1	107 (4)
Stage 2	177 (7)
Stage 3	1,356 (51)
Stage 4	1,038 (39)
Weight on starting ART, kg	58.7 (51.5–67.0)
Starting regimen	
AZT/3TC/EFV	433 (16)
AZT/3TC/NVP	242 (9)
d4T/3TC/EFV	1,179 (44)
d4T/3TC/NVP	825 (31)
Follow-up time on ART, months	11.1 (6.9–18.6)

Continuous variables are given as median (interquartile range). Ordinal and discrete variables are given as *n* (%). 3TC, lamivudine; ART, antiretroviral therapy; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; NVP, nevirapine; WHO, World Health Organization.

Figure 1. Regimen modifications in patients who remain on their original ART regimen at 1, 2 and 3 years of therapy



Number followed	1,293	456	151
Two or more changes including failure, %	1	5	9
Substitution due to toxicity, %	8	9	8
Substitution due to contraindication, %	4	7	11
No changes, %	87	79	72

Analysis was carried out using Stata™ (Version 9, College Station, TX, USA).

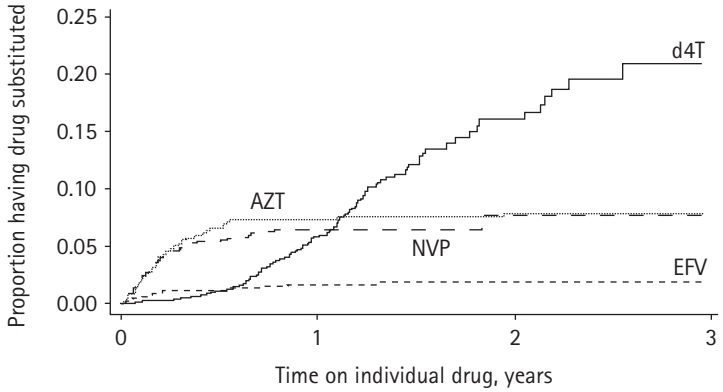
Patient demographics were described using medians and interquartile ranges (IQRs) for continuous variables and counts and percentages for categorical data. Time to treatment substitution or discontinuation were described using Kaplan–Meier analyses. Where >1 causes of failure were analysed together for patients on stavudine, the cumulative incidence for each cause of failure was estimated using a competing risks framework [18]. Rates of substitutions and toxicities are presented per 1,000 patient–years (py). Associations with substitutions were modelled using Cox proportional hazards regression, with the covariates retained in each model being those associated with the outcome in multivariate analysis, or those thought *a priori* to be associated with the outcome. We analysed CD4$^+$ T-cell counts as a binary variable comparing ≥50 to <50 cells/μl. WHO stage at baseline was analysed as an ordinal variable. Age was included as a continuous variable in all multivariate analyses, with results presented per 10-year increment.

Results

The analysis included 950 individuals from Nyanga and 1,729 individuals from Khayelitsha (*n*=2,679; Table 1) with a median follow-up time on ART of 11.1 months (IQR: 6.9–18.6) comprising 3,105 py in total. Most individuals commencing treatment were women (*n*=1,896, 71%), with a median age of 32 years and a median weight of 58.7 kg. The median CD4$^+$ T-cell count at baseline was 85 cells/μl and the median baseline $\log_{10}$ viral load was 5.5. At programme entry, almost 90% (*n*=2,394) of the cohort presented with WHO clinical stage 3 or 4 disease. The most frequent starting regimen comprised d4T, lamivudine (3TC) and efavirenz (EFV) (*n*=1,179, 44%), followed by d4T, 3TC and NVP (*n*=825, 31%) (Table 1). At 3 years, cumulatively 75% (95% confidence interval [CI]: 72–77%) of the cohort were still in the programme in these districts whilst 5% had been transferred to other districts, 15% were known to have died, and the remaining 5% had been lost to follow up.

Of 151 patients remaining in care and who had been on treatment for ≥3 years, 108 (72%) remained on their initial ART regimen in cross-sectional analysis (Figure 1). Eight percent (*n*=12) of individuals had had a single substitution due to toxicity and a further 11% (*n*=17) due to a contraindication. An additional 9%

Figure 2. Estimates of cumulative regimen substitutions due to toxicity by individual drug over a 3-year period



	n				Changed by 36 months, % (95% CI)
AZT	676	469	295	126	7.8 (5.9–10.3)
EFV	1,613	858	334	74	1.9 (1.3–2.8)
NVP	1,062	376	75	44	7.6 (5.3–10.9)
d4T	1,996	782	137	15	20.8 (16.2–26.5)

The graph shows Kaplan–Meier failure estimates by drug. There were no lamivudine substitutions related to toxicity. AZT, zidovudine; CI, confidence interval; d4T, stavudine; EFV, efavirenz; NVP, nevirapine.

(*n*=14) had had >1 drug substitution, including those who had started second-line therapy.

The estimated cumulative substitutions due to toxicity by individual drug are described in Figure 2. There were no instances of regimen modification solely due to toxicity ascribed to 3TC. Thereafter, the least likely drug to be substituted was EFV (25 substitutions, 1.9% at 3 years), with substitutions occurring early in therapy. A larger proportion of individuals were substituted off NVP (*n*=63, 7.6% at 3 years). Again, the majority of these changes occurred within the first few months of therapy and were related to hypersensitivity (including rash and transaminitis). In multivariate analysis, an initial weight below 60 kg was associated with a higher risk of substitution for both NNRTIs (hazard ratio [HR] 2.6 for NVP and 3.1 for EFV; Table 2). Greater age was further associated with NVP substitutions and higher clinical stage was associated EFV substitutions.

A similar proportion of individuals required AZT to be substituted (*n*=47, 7.8% at 3 years), largely because of developing anaemia or neutropenia in the first months of treatment. In multivariate analysis, a baseline $CD4^+$ T-cell count <50 cells/μl was associated with AZT substitution (HR: 2.0; Table 2), whilst age and WHO stage were also found to be associated with this substitution.

Table 2. Multivariate models of associations with toxicity-related regimen modifications in patients on zidovudine, nevirapine or efavirenz

	Zidovudine			Nevirapine			Efavirenz		
Association	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Baseline weight <60 kg				2.6	1.5–4.6	0.001	3.1	1.1–9.4	0.039
Age per 10 year increase	1.3	0.9–1.9	0.113	1.4	1.1–1.9	0.008			
WHO stage per increment	1.9	1.0–3.4	0.045				2.6	1.1–6.2	0.025
Nadir $CD4^+$ T-cell count <50 cells/μl	2.0	1.1–3.7	0.028						

CI, confidence interval; HR, hazard ratio; WHO, World Health Organization.

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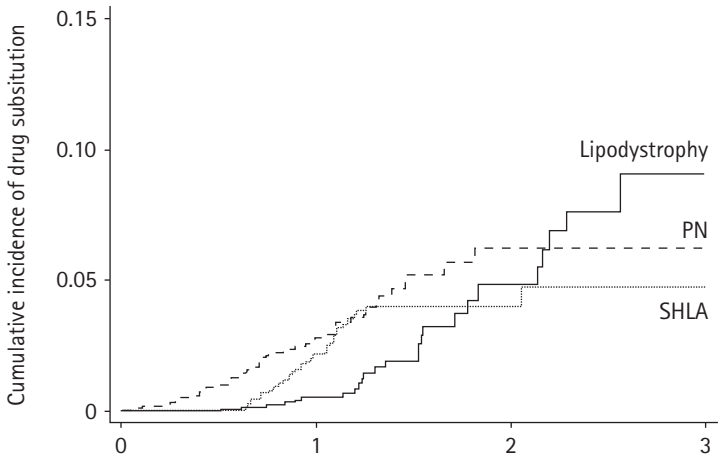
Figure 3. Substitutions of stavudine due to toxicity by indication over a 3-year period



	n				Changed by 3 years, % (95% CI)
PN	1,996	782	137	15	6.2 (4.3–8.5)
SHLA	1,996	782	137	15	4.7 (3.0–6.8)
Lipodystrophy	1,996	782	137	15	9.0 (5.2–14.1)

The graph shows the estimated cumulative incidence of each toxicity. PN, peripheral neuropathy; SHLA, symptomatic hyperlactataemia or lactic acidosis.

The largest number of drug substitutions due to toxicity was in patients on d4T. By 3 years, cumulatively 20.8% of those who originally commenced therapy with d4T had it substituted because of toxicity (125 substitutions; Figure 2), usually with AZT. The timing of d4T substitution depended on the toxicity involved (Figure 3). SHLA were largely confined to a period between 6 and 18 months on therapy and cumulatively 4.7% had changed from d4T for this reason after 3 years on ART. Lipodystrophic body changes resulted in 9.0% of patients stopping d4T by 3 years on ART. These changes were also infrequent until after 6 months on ART. By contrast, substitutions due to peripheral neuropathy were seen from soon after commencement on ART, with 6.2% having had their regimen modified for this reason by 2 years.

The rates for substitutions of d4T were explored for individual toxicities for all patients as well as in subgroups characterized by gender, duration on ART and baseline weight (Table 3). The rate of substitution due to SHLA in women who had been on therapy for >6 months was 7× greater than in men with equivalent exposure (49 vs 7 substitutions/1000 py; rate ratio: 7.5; 95% CI: 1.8–31.2). The rate in women was markedly influenced by weight at baseline; those who weighed ≥75 kg at treatment commencement had a substantially higher rate of substitution beyond 6 months on ART of 184/1000 py than women whose initial weight was <75 kg (21/1000 py; rate ratio 8.8; 95% CI: 4.3–17.7). Although less marked, a similar pattern was noted in the rate of substitution due to lipodystrophy: those at the highest risk were women who weighed more than 75 kg at baseline and who had been on therapy for >6 months. The rate of substitution due to peripheral neuropathy increased slightly after 6 months on therapy, but did not differ markedly by weight or gender.

In multivariate models of associations with substitutions to d4T by indication (Table 4), female gender was strongly associated with substitutions due to both lipodystrophy and SHLA (HRs 10.0 and 10.7 respectively). However initial weight was more strongly associated with substitution due to SHLA than that due to lipodystrophy. Gaining ≥5 kg of weight in the first 3 months on ART was further found to be associated with a 3× increase in the hazard of subsequent substitution of d4T due to SHLA. Age and WHO stage were weakly associated with an increased risk of peripheral neuropathy. In addition, patients in the Nyanga district were more likely to have d4T substituted because of lipodystrophy and less likely to have substitution due to SHLA, whereas there were no differences across clinical sites involving other reasons for d4T substitution.

Table 3. Rates of treatment substitution due to specific toxicities for adults on stavudine categorized by gender, weight and duration on therapy

Toxicity by subgroup at risk	Rate, per 1,000 py	Events, *n* (95% CI)	RR (95% CI)
Symtomatic hyperlactataemia or lactic acidosis			
All durations on ART	19	36 (14–26)	–
All patients <6 months on ART	–	0	–
All patients ≥6 months on ART	36	36 (26–50)	–
Men ≥6 months on ART	7	2 (2–26)	–
Women ≥6 months on ART	49	34 (35–69)	7.5 (1.8–31.2)
Women <75 kg, ≥6 months on ART	21	12 (12–37)	–
Women ≥75 kg, ≥6 months on ART	184	22 (121–279)	8.8 (4.3–17.7)
Lipodystrophy			
All durations on ART	14	26 (9–20)	–
All patients <6 months on ART	–	0	–
All patients ≥6 months on ART	26	26 (18–38)	–
Men ≥6 months on ART	3	1 (0–23)	–
Women ≥6 months on ART	36	25 (24–53)	11.0 (1.5–81.3)
Women <75 kg, ≥6 months on ART	24	14 (14–41)	–
Women ≥75 kg, ≥6 months on ART	92	11 (51–170)	3.8 (1.7–8.3)
Peripheral neuropathy			
All durations on ART	28	53 (21–36)	–
All patients <6 months on ART	17	16 (11–29)	–
All patients, ≥6 months on ART	37	37 (27–51)	2.1 (1.2–3.8)

ART, antiretroviral therapy; CI, confidence interval; RR, rate ratio compared with previous line.

Discussion

This analysis presents novel data on the occurrence of and reasons for antiretroviral drug substitution in two of the longest running public sector ART programmes in Southern Africa. Although overall a high proportion of patients remained on their initial therapy for up to 3 years, there were substantial differences in the tolerability of commonly used first-line antiretroviral drugs, and clearly identifiable risk factors for some of the major toxicities.

The study has a number of strengths. The cohort is representative of many of the settings in the region where treatment access is being rapidly expanded. As these were some of the first cohorts to routinely offer ART in the region, the duration of follow up together with the variability in first-line regimens has allowed an exploration of toxicity for up to 3 years for most of the commonly used drugs. Furthermore, the focus on treatment-limiting toxicities enabled near-complete ascertainment of outcomes. A potential weakness of the study, however, is that although all clinicians were working to common protocols, differences in clinical practice between sites or between clinicians could have resulted in different thresholds for substituting individual drugs.

More than 70% of patients remained on the initial NNRTI-based antiretroviral treatment regimen after 3 years. This compares favourably with the two studies from the UK in which the reported median duration of the first-line ART regimen was 17 months, and 38% of patients had experienced all three classes of antiretrovirals within 2–5 years of commencing therapy [19,20]. Previous estimates of time to treatment substitutions from Europe and North America included a quarter of patients having changed the initial regimen by 1 year [21], a median of 8 months to regimen modification [22], and a quarter having modified their regimen by 6 months on therapy [23]. With the highly regimented approach to therapy promoted in guidelines for resource-limited settings [1], and the limited number of treatment options available, these data suggest that decisions to substitute therapy are taken with caution in these settings.

Despite this caution, a substantial number of patients, up to 28%, did have a drug substitution at least once in the first 3 years of ART. The experience of this cohort suggests that contraindications are more common than treatment-limiting toxicities, most commonly due to a new diagnosis with tuberculosis in patients on NVP, or either pregnancy or a desire to fall pregnant in patients on EFV. This highlights a major

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challenge as a result of tuberculosis in these settings, compounded in countries where NVP-containing, fixed-dose combinations are the mainstay of first-line therapy. The difficulties in ensuring family planning and managing fertility intentions in patients on EFV are also illustrated by these findings.

Toxicities of NNRTIs occurred in the first few months on ART. Although there are existing guidelines for dose reduction of NNRTIs in very small adults, the higher risk of hypersensitivity reactions in patients below 60 kg for both NVP and EFV warrants further exploration, confirming previous findings in the case of NVP [24].

AZT substitution also occurred within the first few months of therapy, with no additional substitutions due to toxicity beyond a year on ART. Patients with more advanced disease, as indicated by either the baseline $CD4^+$ T-cell count or clinical stage, were more likely to develop treatment-limiting haematological toxicity. It is tempting to infer that AZT would be better tolerated if started after individuals have recovered immune function on other first-line drugs. However, there is a concern that after the first few months on ART, monitoring is less intensive in scale-up settings, and even if there were fewer cases of severe anaemia, there might be a higher probability of this being missed in patients many months into therapy.

Almost all substitutions due to toxicity after longer durations on ART were observed in patients on d4T. We found that 21% of individuals commencing stavudine had stopped this drug before 3 years because of toxicity. The replacement drug was usually AZT, which in turn could be recycled in the second-line regimen should this be required. The toxicities and intolerances experienced were those expected from d4T use: peripheral neuropathy, hyperlactataemia and lipodystrophic body changes [3–6]. With the first-line regimens in use in this cohort, clinicians cited these toxicities as a reason for changing therapy only in patients changed from d4T. Previous studies from various settings have also found that severe hyperlactataemia was almost always associated with exposure to d4T [7,25], and have also found risk factors similar to those described here. The markedly increased rate of substitution due to hyperlactataemia for women ≥75 kg on ART for ≥6 months has resulted in changes in local policy to select AZT instead of d4T for these patients. Evidence that the dose escalation of d4T in patients ≥60 kg is not required for virological efficacy could result in the phasing out of the 40 mg formulation and consequently lower rates of toxicity [26]. The higher rate of substitution of d4T due to lipodystrophy in the Nyanga district, and the correspondingly lower rate of substitution due to SHLA, suggests that early substitution for any metabolic toxicities could prevent subsequent, more severe toxicities developing [27].

The different reasons for stopping stavudine because of toxicity could be related to the same underlying disease process. The associations with each toxicity-mediated substitution could therefore potentially be biased by censored observations (related to stopping stavudine for other toxicities). We explored estimating the associations jointly across all three toxicity-related reasons for stopping stavudine [28] and the results from this exercise were consistent with those presented here.

In summary, we found that a high proportion of treatment-naive adult patients are able to tolerate their initial ART regimen for up to 3 years in this large South African public-sector cohort. However, treatment-limiting toxicities are present and continue to accumulate with time in the case of d4T. Because of limited ART options, this and other substitutions might compromise future therapy. Access to alternative NRTIs would provide additional options to clinicians and patients,

Table 4. Multivariate models of associations with toxicity-related regimen modifications in patients on stavudine, by specific toxicity

	Lipodystrophy			Hyperlactataemia/lactic acidosis			Peripheral neuropathy		
Association	HR	95% CI	*P*-value	HR	95% CI	*P*-value	HR	95% CI	*P*-value
Female gender	10.0	1.3–74.5	0.025	10.7	1.5–79.0	0.02	–	–	–
Weight									
<60 kg	1.0	–	–	1.0	–	–	–	–	–
60–74.9 kg	0.6	0.2–1.9	0.017	5.7	1.5–21.0	<0.001	–	–	–
≥75 kg	4.1	1.6–10.5	–	36.1	10.6–122.8	–	–	–	–
Nyanga district	3.5	0.9–12.8	0.062	0.4	0.2–0.9	0.026	–	–	–
Weight gain first 3 months ≥5 kg	–	–	–	3.1	1.5–6.2	0.002	–	–	–
Age per 10-year increase	–	–	–	–	–	–	1.4	1.0–1.9	0.034
WHO stage per increment	–	–	–	–	–	–	1.6	1.0–2.5	0.040

CI, confidence interval; HR, hazard ratio; WHO, World Health Organization.

but regrettably these agents (for example tenofovir and abacavir) are currently either too costly or are not widely available in resource-limited settings. Until alternative agents are available, clinicians should be encouraged to be aware of d4T-related toxicity and substitute AZT earlier rather than later. Avoiding d4T in women ≥75 kg and using lower dose d4T might also contribute to reductions in severe toxicity.

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Outcomes of Nevirapine- and Efavirenz-Based Antiretroviral Therapy When Coadministered With Rifampicin-Based Antitubercular Therapy

Paper overview

This analysis explores the impact of tuberculosis co-infection on ART outcomes, as tuberculosis is one of the most important contextual co-morbidities in the region. The analysis is directed towards an important area of clinical uncertainty, which is the choice of NNRTI in patients on ART while also on treatment for tuberculosis.

Contribution to the thesis and novelty

The analysis addresses the third objective, which is to describe the impact of concomitant tuberculosis on ART treatment outcomes. Although the paper and data are oriented to address the question of the choice of NNRTI, all the outcomes described in the first paper in this thesis are also described in this paper in patients with and without concomitant tuberculosis. The analysis was able to demonstrate that co-infection with tuberculosis does not compromise ART outcomes, except for virological response in co-infected patients initiating NVP-based ART. At the time of publication it was the largest study to compare outcomes in these groups of patients, and the first to suggest inferior outcomes for co-infected patients initiating NVP-based ART compared to patients who were not on tuberculosis treatment.

Contributions of candidate

These data were first presented at the 38th Union World Conference on Lung Health in November 2007. The candidate was co-responsible for the data management in the cohort from 2002, and was responsible for all the analyses in the paper. The candidate was primarily responsible for the drafting of all versions of the manuscript, which included integrating comments from co-authors.

Publication status

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ORIGINAL CONTRIBUTION

Outcomes of Nevirapine- and Efavirenz-Based Antiretroviral Therapy When Coadministered With Rifampicin-Based Antitubercular Therapy

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Context Rifampicin-based antitubercular therapy reduces the plasma concentrations of nevirapine and efavirenz. The virological consequences of these interactions are not well described.

Objective To assess the effectiveness and tolerability of concomitant efavirenz- or nevirapine-based combination antiretroviral therapy and rifampicin-based antitubercular therapy.

Design, Setting, and Participants Cohort analysis of prospectively collected routine clinical data in a community–based South African antiretroviral treatment program. Antiretroviral treatment-naive adults enrolled between May 2001 and June 2006 were included in the analysis, and were followed up until the end of 2006.

Interventions Patients starting antiretroviral therapy with or without concurrent antitubercular therapy received either efavirenz or nevirapine at standard doses. Patients developing tuberculosis while taking antiretroviral therapy that included nevirapine were either changed to efavirenz or continued taking nevirapine.

Main Outcome Measures Viral load of 400 copies/mL or more after 6, 12, and 18 months of antiretroviral therapy; time to the first viral load of 400 copies/mL or more; time to confirmed virological failure (2 consecutive values ≥5000 copies/mL); time to death; and time to treatment-limiting toxicity were assessed.

Results The analysis included 2035 individuals who started antiretroviral therapy with efavirenz (1074 with concurrent tuberculosis) and 1935 with nevirapine (209 with concurrent tuberculosis). There were no differences in time to death or substitution of either antiretroviral drug for toxicity with and without concurrent tuberculosis. Patients starting nevirapine with concurrent tuberculosis were at a higher risk of elevated viral load most notably at 6 months (16.3%; 95% confidence interval [CI], 10.6%-23.5%) than those without tuberculosis (8.3%; 95% CI, 6.7%-10.0%; adjusted odds ratio [OR], 2.1; 95% CI, 1.2-3.4; and in the combined estimate, adjusted OR, 1.7; 95% CI, 1.2-2.6). In the time-to-event analysis of confirmed virological failure (2 consecutive values of ≥5000 copies/mL), patients starting nevirapine with concurrent tuberculosis developed virological failure sooner (adjusted hazard ratio [HR] 2.2; 95% CI, 1.3-3.7). There were no differences between patients starting efavirenz with and without concurrent tuberculosis (adjusted OR, 1.1; 95% CI, 0.8-1.5 [combined estimate] and adjusted HR, 1.1; 95% CI, 0.6-2.0, respectively). There was no difference in time to virological rebound in patients free of tuberculosis and those developing tuberculosis during follow-up while taking nevirapine (adjusted HR, 1.0; 95% CI, 0.5-2.0) or efavirenz (adjusted HR, 0.8; 95% CI, 0.4-1.7).

Conclusion In this cohort study, virological outcomes were inferior when nevirapine-based antiretroviral therapy was commenced while taking antitubercular treatment (vs without concurrent tuberculosis) but comparable when starting efavirenz-based antiretroviral therapy (vs without concurrent tuberculosis) or when tuberculosis developed while taking established nevirapine- or efavirenz-based therapies.

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ANTIRETROVIRAL THERAPY (ART) programs are rapidly being scaled up in resource-limited countries, where tuberculosis is the most common opportunistic infection.[1] Combination ART is frequently initiated when patients are being treated for tuberculosis.[2,3] Although ART reduces tuberculosis incidence, tuberculosis continues to occur at considerably higher rates than in individuals who are not infected with human immunodeficiency virus (HIV).[1-4] Coadministration of ART and antitubercular therapy may be complicated by shared toxicity, notably hepatotoxicity,[5] or by adverse drug interactions. Rifampicin is a potent inducer of cytochrome P450 enzymes, which metabolize many drugs including nonnucleoside reverse transcriptase inhibitor (NNRTI) antiretroviral agents. The NNRTIs are recommended as components of initial combination ART regimens in the public health approach advocated by the World Health Organization (WHO).[6]

Of the 2 available NNRTIs, efavirenz is preferred for coadministration with rifampicin[6,7] because the reduction in the concentration of efavirenz is more modest, efavirenz has a lower risk of hepato-

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toxicity, and there are several studies showing good ART outcomes with efavirenz.[8,9] Some experts recommend increasing the dose of efavirenz when coadministered with rifampicin,[6] but evidence, including data from a randomized controlled trial,[10] suggests that standard doses are adequate (although there are concerns that there are insufficient data on patients weighing more than 60 kg).[7]

Nevirapine (often in fixed-dose combination formulations) is the most widely used NNRTI in resource-limited countries because it is much cheaper than efavirenz and, unlike efavirenz, is suitable for women of childbearing potential because it is not a known teratogen. In many countries, it is the only available NNRTI. Pharmacokinetic studies show a more significant reduction in plasma nevirapine concentrations (20%-55% reduction in serum concentrations or the area under the curve) compared with efavirenz when coadministered at standard doses with rifampicin.[9,11-16] Nevirapine has a higher risk of hepatotoxicity than efavirenz, although only a small proportion of patients develop clinical hepatitis.[17-19] There are 3 small published studies (32 patients from Spain[20] and 70 patients[21] and 111 patients from Thailand[22]) that suggest that nevirapine can be safely and effectively coadministered with rifampicin. However, the findings from the Thai studies may not be generalizable to other populations due to ethnic differences in drug effects and the low body weight of the patients, and the Spanish study was retrospective without a comparison group.

Thus a need for more studies exists, particularly from Africa where approximately 85% of HIV-associated cases of tuberculosis occur.[4] Our primary objective was therefore to assess the virological outcomes of concomitant efavirenz- or nevirapine-based combination ART and rifampicin-based antitubercular therapy in a cohort of South African patients from a public sector ART program established in 2001.[23]

METHODS

Setting

This study was conducted at 3 community health centers in the Cape Town township of Khayelitsha, where ART has been available since May 2001, with the number of patients starting ART increasing dramatically in recent years. ART-naive individuals enrolled between May 2001 and June 2006 were included in the analysis and were followed up until the end of 2006. The community of 400 000 inhabitants has an extremely high burden of both HIV and tuberculosis, with antenatal HIV seroprevalence of more than 30%,[23,24] and tuberculosis case-finding exceeding 1500 per 100 000 annually.[2] This government program has been supported by Médecins Sans Frontières since inception.

The cohort received approval in 2005 from the University of Cape Town ethics committee for analyses (including those with a view to scientific publication) based on anonymized routine clinical data without requiring informed consent. All data in this analysis were anonymized and had been collected as part of the routine standard of care intervention.

Antiretroviral Therapy Program

Patients were referred to the dedicated HIV services within these community health centers from local clinics and hospitals, as well as from the tuberculosis services and the prevention of mother-to-child transmission program. Once referred, patients accessed treatment based on clinical eligibility, treatment readiness, and clinical severity. Race is not routinely measured as part of clinical or administrative data, but the study site is located in a township in which residents are of black African or mixed ancestry, which describes the patients represented in analyses herein. Women who had been exposed through a regimen intended to prevent mother-to-child transmission to short-course zidovudine or peripartum nevirapine[25] were offered the same first-line ART as other women with and without concurrent tuberculosis.

Antiretroviral drugs were provided weekly or fortnightly for the first 2 months of ART, then monthly until the first suppressed viral load, and thereafter either monthly or bimonthly. Patients were seen by a nurse or physician at each follow-up visit and either received the drugs during the consultation or from a dedicated dispensing room immediately after the consultation. Patients were all provided with weekly pillboxes.

There is a structured adherence promotion program at the antiretroviral clinics, which has previously been described.[26] Adherence is assessed during consultations by pill counts and self-report, especially shortly after initiation of ART and if patients default or experience virological failure. Quantitatively, adherence is indirectly reflected by viral load outcomes and retention in care.

The first-line ART regimen has always consisted of an NNRTI (either efavirenz or nevirapine) together with 2 nucleoside reverse transcriptase inhibitors. Guidelines in use strongly recommended prescribing efavirenz with rifampicin-based antitubercular therapy until 2004 when provincial guidelines changed to allow clinicians to select either nevirapine or efavirenz.[27] Thereafter, clinical practice in the choice of NNRTI with antitubercular therapy varied, with some clinicians continuing to prescribe efavirenz while others prescribed nevirapine.

Standard doses of both efavirenz (600 mg daily) and nevirapine (lead-in dose of 200 mg daily for 2 weeks followed by 200 mg every 12 hours) were used with concurrent tuberculosis treatment in keeping with provincial, national, and international guidelines.[6,27,28] The clinical protocols provide for monitoring of viral load and CD4 cell count every 6 months. Baseline viral loads are no longer universally drawn in treatment-naive adults. Patients are deemed eligible for ART when their CD4 cell count approaches or falls below 200 cells/μL or when they have a WHO clinical stage IV illness other than extrapulmonary tuberculosis. The local definition of virological failure is 2 consecutive viral load measurements of 5000 copies/mL or higher. Viral load tests were performed by the National Health Laboratory Service, initially using the NucliSens HIV-1 QT assay and later the NucliSens EasyQ HIV-1 assay (bioMérieux, Boxtel, the Netherlands).

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Tuberculosis Services

Tuberculosis medication was provided daily (5 days a week) at 8 dedicated tuberculosis clinics in the community and was directly observed either by clinic staff or by trained community-based tuberculosis treatment supporters. Fixed-dose combinations are used to promote adherence (for new tuberculosis cases, these comprise rifampicin, pyrazinamide, isoniazid, and ethambutol for 2 months, followed by rifampicin and isoniazid for 4 months). Tuberculosis was diagnosed according to standard guidelines, with either positive microscopy for acid-fast bacilli, a positive culture of *Mycobacterium tuberculosis*, or after the application of an algorithm for identifying smear-negative tuberculosis.[29]

Data Management and Analysis

Routine clinical data have been prospectively entered into an electronic patient information system, which is regularly validated for accuracy and complete-

Figure 1. Inclusion of Patients in the Analysis

ART indicates antiretroviral therapy; TB, tuberculosis.
[a]Additional censoring at each duration of follow-up was due to the patients not being in care for long enough at the close of the study.

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ness. In this analysis, all treatment-naive individuals 14 years or older, with a CD4 cell count lower than 250 cells/μL, who started receiving NNRTI-based ART by June 30, 2006, were included. Patients were excluded if they had concurrent tuberculosis at the time that they started ART, but subsequently discontinued tuberculosis therapy within 14 days of starting ART. The remaining patients were classified into 4 groups based on whether ART initiation overlapped with concurrent treatment for tuberculosis and based on which NNRTI was part of their starting ART regimen (FIGURE 1). Patients were followed up until the earliest of the following possibilities: loss to the program (death, lost to follow-up, transferred out); interruption of ART therapy for any reason; substitution of the initial NNRTI due to toxicity or contraindications (eg, efavirenz changed to nevirapine in pregnancy); starting tuberculosis treatment due to a subsequent diagnosis; or the last visit prior to December 31, 2006. Patients were classified as lost to follow-up after 6 months without a visit to the service. Viral loads were classified as 6-, 12-, or 18-month values based on the duration closest to the actual dates of the test, provided the test was performed within 3 months of the designated duration.

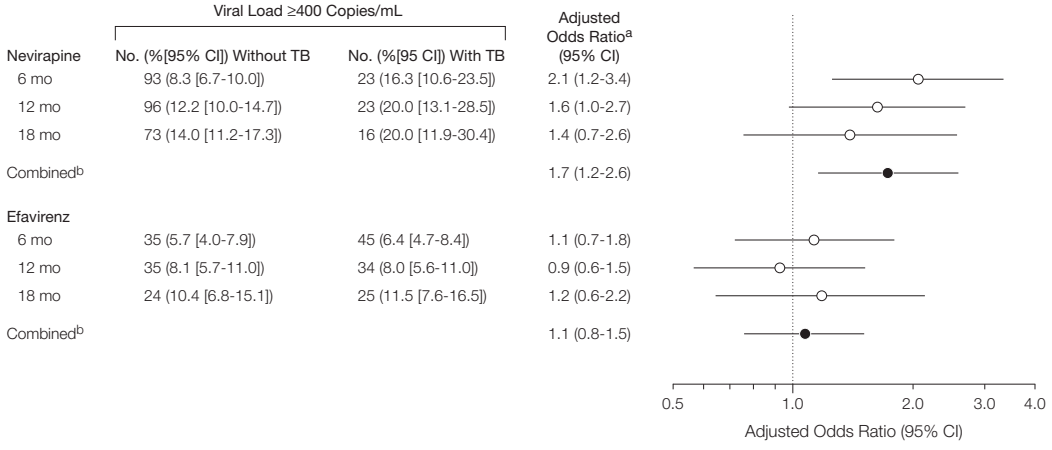
The analysis was conducted between October 2007 and February 2008. Baseline characteristics were described as medians with interquartile ranges for continuous variables and as proportions with

Table 1. Baseline Characteristics of Patients Starting Antiretroviral Therapy Relative to the Nonnucleoside Reverse Transcriptase Inhibitor Used and Concurrent Tuberculosis

	Tuberculosis			No Tuberculosis		
	Nevirapine (n = 209)[a]	Efavirenz (n = 1074)[b]	*P* Value[c]	Nevirapine (n = 1726)[d]	Efavirenz (n = 961)[e]	*P* Value
Age, median (IQR), y	32 (28-37)	32 (28-38)	.47	31 (27-37)	34 (29-40)	<.001
CD4 cell count, median (IQR), cells/μL	80 (42-137)	61 (27-117)	.002	116 (58-167)	93 (37-155)	<.001
Viral load, median (IQR), $\log_{10}$ copies/mL	5.3 (4.6-5.7)	5.3 (4.8-5.7)	.28	5.0 (4.4-5.5)	5.1 (4.6-5.5)	.04
Weight, median (IQR), kg	56 (51-65)	56 (49-63)	.45	60 (53-69)	59 (52-68)	.009
ALT, median (IQR), UL	24 (18-33.5)	27 (19-40)	.07	23 (18-33)	32 (21-53)	<.001
Duration of TB treatment, median (IQR), d	87 (60-135)	73 (44-115)	<.001			
Women, % (95% CI)	73.7 (67.2-79.5)	62.1 (59.1-65.0)	<.001	80.0 (78.0-81.9)	57.1 (53.9-60.3)	<.001
AIDS diagnosis, % (95% CI)	55.0 (48.0-61.9)	58.1 (55.1-61.1)	.002	27.3 (25.2-29.5)	37.9 (34.8-41.0)	<.001
Zidovudine in starting regimen, % (95% CI)	4.3 (1.5-7.1)	14.4 (12.3-16.5)	<.001	12.4 (10.8-14.0)	31.3 (28.4-34.3)	<.001
Extrapulmonary TB, % (95% CI)	37.3 (30.7-44.3)	37.2 (34.3-40.2)	.98			

Abbreviation: ALT, alanine aminotransferase; CI, confidence interval; IQR, interquartile range; TB, tuberculosis.
[a]The number of patients with ALT values was 128; weight, 203; and viral load, 181.
[b]The number of patients with ALT values was 688; weight, 1054; and viral load, 806.
[c]Rank-sum test for continuous variables, and χ^2 test for binary variables.
[d]The number of patients with ALT values was 1107; weight, 1668; and viral load, 1314.
[e]The number of patients with ALT values was 489; weight, 943; and viral load, 757.

Figure 2. Failure to Suppress Viral Load in Patients With Concurrent Tuberculosis at the Start of Antiretroviral Therapy vs Those Without Concurrent Tuberculosis



CI indicates confidence interval; TB, tuberculosis.
[a]Adjusted for age, sex, and baseline CD4 cell count. The adjusted odds ratios and 95% CIs were rounded to 1 decimal.
[b]Combined odds ratios were calculated with generalized estimating equation and an exchangeable correlation matrix.

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Table 2. Multivariate Model of Associations With Failure to Suppress Viral Load[a]

	OR (95% CI)	*P* Value
Women	1.0 (0.7-1.2)	.73
<30 y	1.4 (1.1-1.8)	.003
Baseline CD4 cell count, per 25 cells/μL increase	0.9 (0.9-1.0)	.004
NNRTI and TB at start of ART		
Efavirenz, no TB	1 [Reference]	
Efavirenz and prevalent TB[b]	1.1 (0.8-1.6)	<.001
Nevirapine, no TB	1.6 (1.1-2.2)	
Nevirapine and prevalent TB[b]	3.2 (2.0-5.2)	
Duration on ART, mo		
6	1 [Reference]	
12	1.5 (1.2-1.7)	<.001
18	1.8 (1.4-2.1)	
Weight at baseline, kg		
<60	1 [Reference]	
60-79.9	1.2 (0.9-1.5)	.06
≥80	1.6 (1.1-2.4)	
Year of ART initiation		
2001-2002	1 [Reference]	
2003	0.7 (0.4-1.2)	
2004	0.7 (0.5-1.1)	.08
2005	0.6 (0.4-0.8)	
2006	0.7 (0.4-1.2)	

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; NNRTI, nonnucleoside reverse transcriptase inhibitor; OR, odds ratio; TB, tuberculosis.
[a] Model included 5283 observations involving 2670 patients.
[b] Patients had received concurrent treatment for tuberculosis for at least 14 days at the time of starting ART.

exact binomial confidence intervals (CIs) for categorical variables, compared between groups, respectively, through rank sum and χ^2 statistics.

The proportions of patients with viral loads of 400 copies/mL or more were calculated at each duration in each of the 4 groups (Figure 1). The odds of a value at or higher than this threshold in patients who were receiving concurrent tuberculosis treatment when starting ART were compared with those who were not, in separate multivariate logistic regression models at each duration for each NNRTI. Pooled odds ratios (ORs) across all durations were additionally determined for each NNRTI and for all 4 groups together with generalized estimating equation repeated-measures analyses accounting for intraindividual correlation through an exchangeable correlation matrix.

For all multivariate models, variables were included based on a priori considerations, if they were themselves associated with the outcome or if they changed the other associations in the model.

Kaplan-Meier failure estimates were determined comparing the 2 tuberculosis exposure groups receiving each NNRTI for time to death, time to NNRTI substitution due to toxicity, time to the first viral load at the threshold of 400 copies/mL or more (restricted to values beyond 30 days of follow-up), time to loss to follow-up, and time to virological failure as defined above. In the analysis of time to death, patients were not censored with subsequent tuberculosis episodes or with changes or interruptions to the NNRTI. In the analysis of time to treatment-limiting toxicity, patients starting ART with TB were censored at the end of the initial tuberculosis episode. Log-rank statistics and adjusted hazard ratios (HRs) from Cox proportional hazard models were determined for each comparison. The proportional hazards assumptions were validated for the Cox models based on Schoenfeld residuals. The CD4 cell count changes relative to baseline were compared at 18 months in separate multivariate linear regression models for each NNRTI.

A second analysis was performed in patients who did not have tuberculosis at the start of ART, in which the time to virological rebound was determined from the time of the first viral load lower than 400 copies/mL. Concurrent tuberculosis treatment as a result of incident tuberculosis during follow-up was included as a time-varying exposure in both Kaplan-Meier estimates and multivariate Cox proportional hazard models. Patients developing tuberculosis remained in this exposure group even if they were followed up beyond the end of the tuberculosis treatment episode. Follow-up was censored in the same way as in the first analysis, except in the case of incident tuberculosis whereby patients were censored if a second episode of tuberculosis occurred during follow-up.

Using the 6-month follow-up duration, the 141 and 1126 patients assessed who started nevirapine-based ART with or without concurrent antitubercular therapy would ensure 88% power to detect a 10% decline in viral load suppression in the group receiving concurrent tuberculosis treatment, assuming a 90% suppression in the reference group ($\alpha = .05$)

The analysis was conducted using Stata statistical software, 10.0 (StataCorp Inc, College Station, Texas). In each analysis, only observations with complete data on the outcomes and covariates were used, while the completeness of both the main outcome and covariate data are reported (Figure 1 and TABLE 1, respectively). All statistical tests were 2-sided.

RESULTS

The proportion of patients starting ART while receiving concurrent tuberculosis therapy increased from 21% (17 of 80) in 2001 to 40% (439 of 1099) in 2006. Since 2004, the majority of patients initiated nevirapine-based ART, although in patients with concurrent tuberculosis, efavirenz use has still predominated.

Of 4117 individuals who met the initial inclusion criteria, 2687 were not re-

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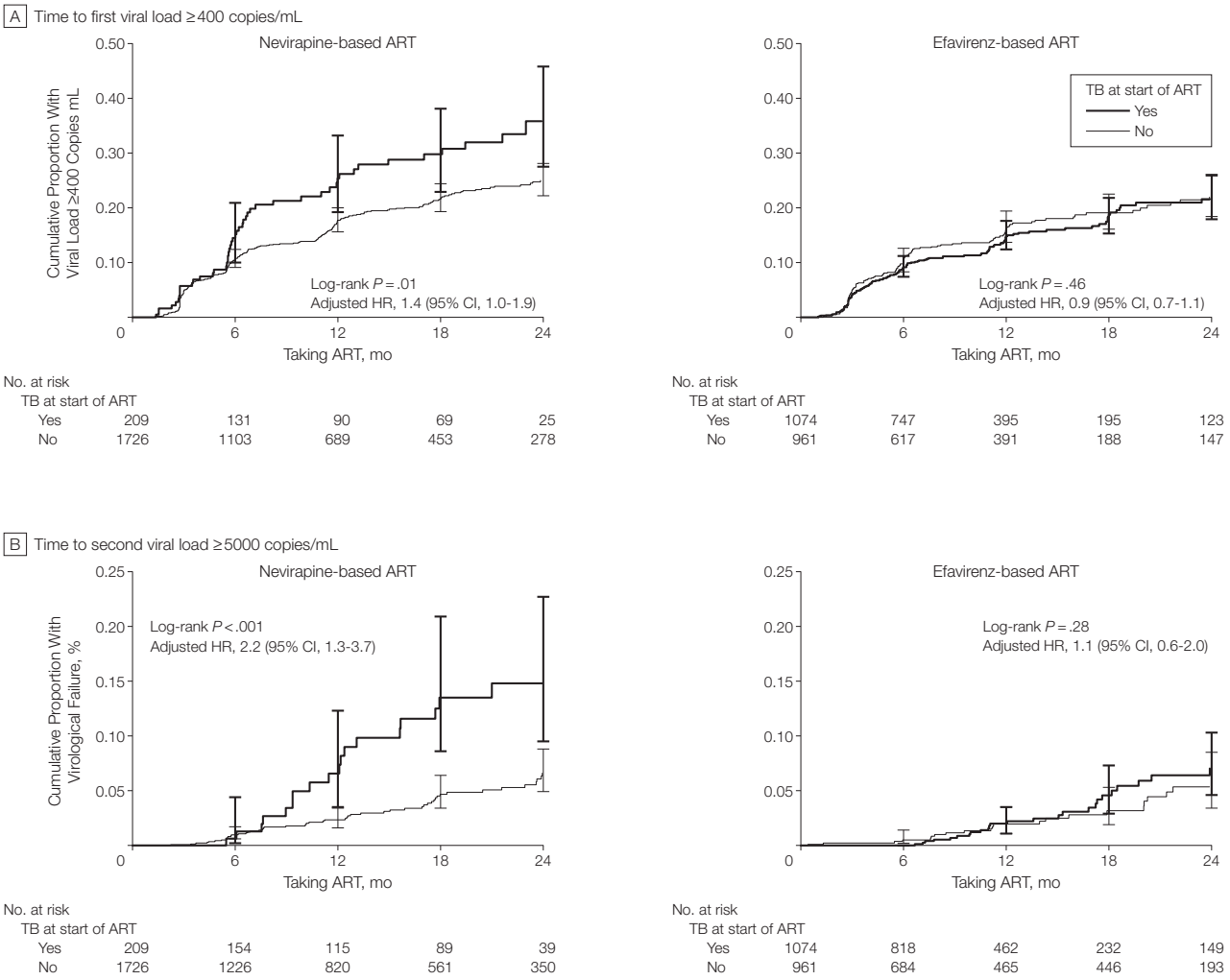
ceiving tuberculosis treatment at the start of therapy (Figure 1). Of the remaining 1430 who started ART while receiving concurrent tuberculosis therapy, 249 started taking nevirapine-based ART and 1181 started taking efavirenz-based ART. Of these, 209 and 1074 patients, respectively, had overlapping treatment for at least 14 days. Overall, in all groups at all durations of follow-up, between 83% and 96% of patients who were eligible for virological assessment and inclusion in the analysis were assessed.

Patients with concurrent tuberculosis were compared between NNRTI groups at the start of ART (Table 1) and were similar with respect to age, baseline viral load where available, weight (median of 56 kg in both groups with concurrent tuberculosis), alanine aminotransferase where available, and the proportion with extrapulmonary tuberculosis. Patients with tuberculosis initiating nevirapine had a slightly higher CD4 cell count (80 vs 61 cells/μL, $P = .002$) and had been receiving tuberculosis therapy for slightly longer than those initiating efavirenz (87 vs 73 days, $P < .001$). They were also more likely to be women (73.7% vs 62.1%, $P < .001$ [because efavirenz is teratogenic, it is often avoided in women of childbearing potential]), less likely to have started taking zidovudine (4.3% vs 14.4%, $P < .001$), and were less likely to have a stage IV–defining illness (55.0% vs 58.1%, $P = .002$). Findings in the same directions were observed comparing baseline characteristics between NNRTI groups without concurrent tuberculosis (Table 1), except that patients initiating efavirenz were older and had higher baseline aminotransferase values when available.

Overall, the proportion of patients with elevated viral loads was lowest at 6 months while taking ART in all 4 groups (FIGURE 2). There was no discernable dif-

Figure 3. Cumulative Estimates of Time to Elevated Viral Load and Virological Failure



ART indicates antiretroviral therapy; CI, confidence interval; HR, hazard ratio; TB, tuberculosis. Error bars indicate 95% CIs. Adjusted for age, sex, and baseline CD4 cell count.

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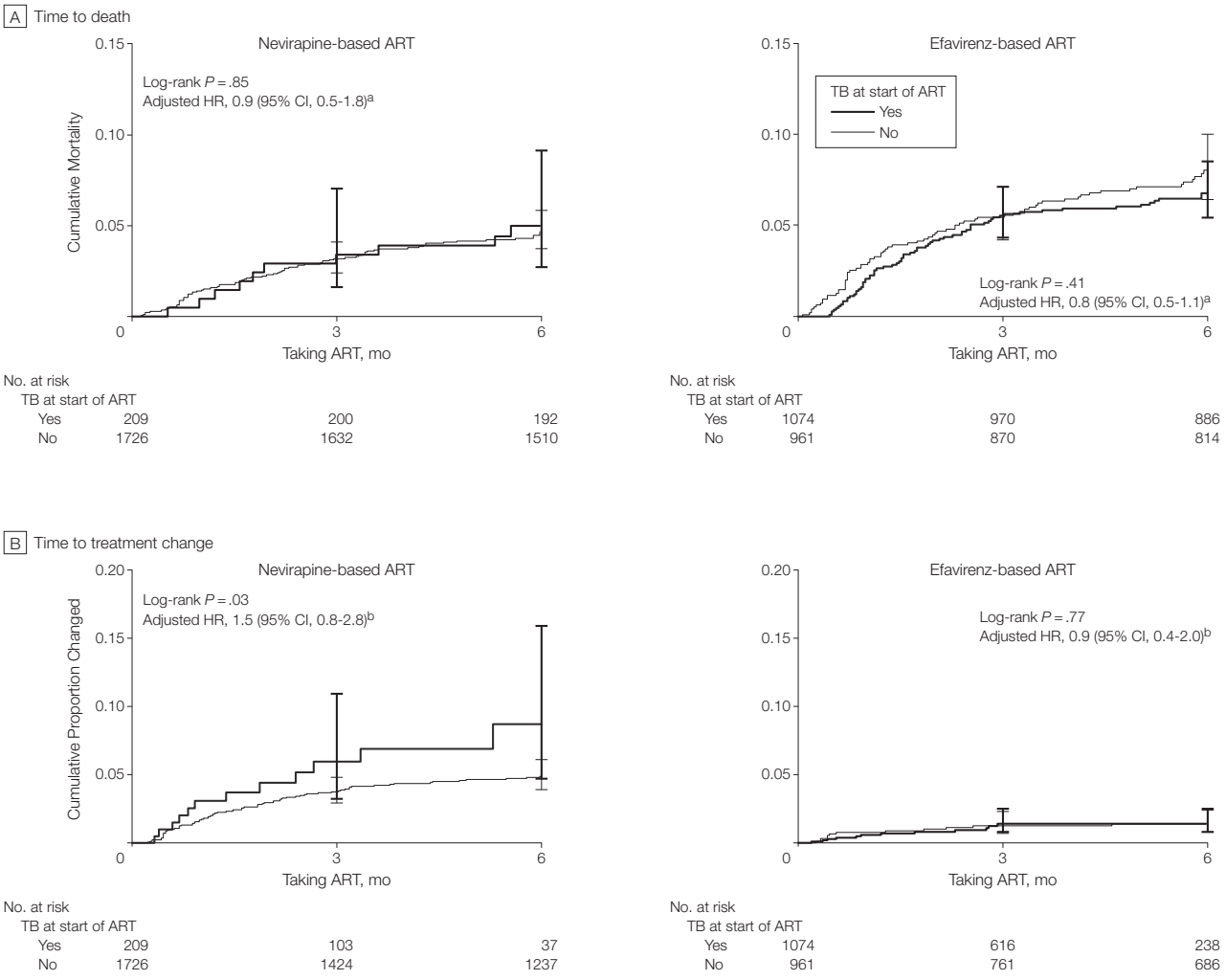
ference in this measure based on baseline tuberculosis therapy status in patients initiating efavirenz (combined adjusted OR, 1.1; 95% CI, 0.8-1.5). However, a higher proportion of patients initiating nevirapine with initial concurrent tuberculosis had elevated viral loads during follow-up than those without concurrent tuberculosis. This was most notable at 6 months (16.3%; 95% CI, 10.6%-23.5% vs 8.3%; 95% CI, 6.7%-10.0%; adjusted OR, 2.1; 95% CI, 1.2-3.4), and in the combined estimate (adjusted OR, 1.7; 95% CI, 1.2-2.6).

A model combining all the groups together demonstrated clearly the inferior virological outcomes (failure to suppress viral load) in the group starting to take both nevirapine and tuberculosis treatment relative to the efavirenz groups (eg, adjusted OR, 3.2; 95% CI, 2.0-5.2 for the group initiating nevirapine and tuberculosis treatment vs the group initiating efavirenz without concurrent tuberculosis at the start of ART, TABLE 2). The outcomes associated with receiving nevirapine were inferior even without concurrent tuberculosis (adjusted OR, 1.6; 95% CI, 1.1-2.2 for the group initiating nevirapine without concurrent tuberculosis vs the group initiating efavirenz without concurrent tuberculosis). Age younger than 30 years, a low baseline CD4 cell count, and increasing baseline weight were independently associated with failure to suppress viral load in this model. The use of zidovudine over stavudine in the starting regimen was not associated with the outcome; therefore, this was not included in the final model. We found little evidence for interactions between the NNRTI used or con-

Figure 4. Cumulative Estimates of Time to Death and Regimen Change Due to Toxicity



ART indicates antiretroviral therapy; CI, confidence interval; HR, hazard ratio; TB, tuberculosis. Error bars indicate 95% CIs.
[a] Adjusted for age, sex, baseline CD4 cell count, and year of ART initiation.
[b] Adjusted for age, sex, and baseline CD4 cell count.

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current tuberculosis and any of the other exposure variables in the model (all *P* values >.05 [likelihood ratio test]). In alternate models that included available baseline viral load data, this was independently associated with failure to suppress subsequent viral loads (adjusted OR, 1.3 for each $\log_{10}$ increase in the baseline value, 95% CI, 1.1-1.6) and did not confound the associations between this outcome—choice of NNRTI—and concomitant tuberculosis.

The time-to-event analysis of failure to suppress viral load (FIGURE 3A) provided adjusted HR estimates consistent with the pooled adjusted OR estimate above (for nevirapine, adjusted HR, 1.4; 95% CI, 1.0-1.9; for efavirenz, adjusted HR, 0.9; 95% CI, 0.7-1.1). The difference in the case of receiving nevirapine with and without concurrent tuberculosis treatment was more marked when assessing time to confirmed virological failure (adjusted HR, 2.2; 95% CI, 1.3-3.7; Figure 3B). Concurrent tuberculosis treatment was not associated with time to confirmed virological failure in patients starting efavirenz-based ART (adjusted HR, 1.1; 95% CI, 0.6-2.0).

Other Outcome Measures

In comparing other outcomes, there was no difference after adjustment between the groups receiving tuberculosis treatment vs those without concurrent tuberculosis for each NNRTI in regard to mortality (adjusted HR for nevirapine, 0.9; 95% CI, 0.5-1.8; adjusted HR for efavirenz, 0.8; 95% CI, 0.5-1.1; FIGURE 4A), or in regard to time to toxicity-mediated NNRTI substitution (adjusted HR for nevirapine, 1.5; 95% CI, 0.8-2.8; adjusted HR for efavirenz, 0.9; 95% CI, 0.4-2.0; Figure 4B). In patients without concurrent tuberculosis, those patients receiving nevirapine were more likely to have their therapy substituted due to toxicity compared with those receiving efavirenz (cumulative proportion receiving nevirapine having treatment substitution by 6 months, 4.9%; 95% CI, 3.9%-6.1% vs 1.4%; 95% CI, 0.8%-2.4% in the case of efavirenz).

For both nevirapine and efavirenz, concurrent tuberculosis treatment at the start of ART was associated with an additional gain of 29 cells/μL in CD4 cell count at 18 months compared with baseline, adjusted for age, sex, and baseline CD4 cell count (95% CI, 1-56 for nevirapine; 95% CI, 6-51 for efavirenz), in comparison with patients taking nevirapine and efavirenz without tuberculosis.

In the 4 groups combined, viral load suppression to less than 400 copies/mL was 92.4% (95% CI, 91.3%-93.4%) at 6 months, 89.3% (95% CI, 87.8%-90.7%) at 12 months, and 86.8% (95% CI, 84.6%-88.8%) at 18 months of ART. Cumulative loss to follow-up was 5.6% (95% CI, 4.4%-7.5%) at 24 months of ART and was comparable between the 4 groups.

Incident Tuberculosis in Patients Already Receiving NNRTI-Based ART

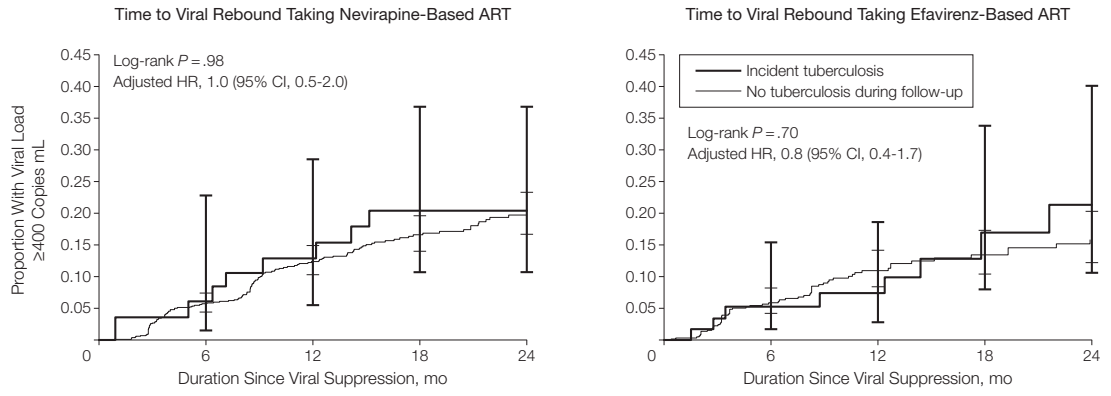
The final analysis compared the time to virological rebound between patients remaining free of tuberculosis during follow-up and those who were initially free of tuberculosis but subsequently started tuberculosis treatment due to a new tuberculosis episode (FIGURE 5). There was no difference in time to rebound between the groups among those who did and did not experience incident tuberculosis receiving either NNRTI (adjusted HR, 1.0; 95% CI, 0.5-2.0 for nevirapine; adjusted HR, 0.8; 95% CI, 0.4-1.7 for efavirenz).

COMMENT

Main Findings

Coadministered rifampicin-based antitubercular therapy at ART initiation resulted in higher probabilities of an elevated viral load or virological failure in the first 2 years of therapy in patients taking nevirapine-based ART but not in patients who started efavirenz-based ART. In spite of these differences, viro-

Figure 5. Cumulative Estimates of Time to Elevated Viral Load Since First Suppressing Viral Load (≥ 400 copies/mL) in Patients Without Tuberculosis at the Start of Antiretroviral Therapy, Stratified by Subsequent Incident Tuberculosis



No. at risk										
Incident tuberculosis	27	40	35	28	17	56	49	38	20	15
No tuberculosis during follow-up	1136	771	534	336	184	634	428	262	167	133

ART indicates antiretroviral therapy; CI, confidence interval; HR, hazard ratio. Error bars indicate 95% CIs. Adjusted for age, sex, and baseline CD4 cell count.

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logical outcomes were good, with 80% of patients in the initial nevirapine-rifampicin group being virologically suppressed at 18 months' duration of ART. For both NNRTIs, incident tuberculosis during follow-up did not result in an increased risk of virological rebound.

Underlying Mechanisms

The differential findings between the group starting nevirapine with prevalent tuberculosis and those developing tuberculosis once already established on ART could be the result of the limited power of the latter analysis to detect a difference due to the inclusion of fewer patients with incident tuberculosis. An alternative explanation, however, is a drug interaction mediated by rifampicin during the lead-in dosing phase of nevirapine. A 2-week lead-in period of once daily instead of twice daily dosing is recommended to allow for the autoinduction of the cytochrome P450 enzyme system by nevirapine. In patients taking rifampicin, the system is however already induced. A recent Malawian study[30] found that 59% of patients coinfected with HIV and tuberculosis had subtherapeutic nevirapine concentrations during the lead-in dosing phase. A Thai study that compared patients initiating efavirenz-based or nevirapine-based ART with concurrent tuberculosis reported an OR between these groups for achieving a viral load lower than 50 copies/mL at 48 weeks of 0.590 (95% CI, 0.302-1.153)[22] but was based on smaller numbers of patients.

Strengths and Limitations of This Study

The published literature on the virological efficacy of standard doses of NNRTI-based ART coadministered with rifampicin is sparse, but the data are generally encouraging. The existing studies have, however, been limited by small sample sizes[8,20,21,30,31] or by the failure to include a control group.[30,31]

Key strengths of our study include the large sample size of patients starting ART, a good follow-up rate, and the assessment of virological responses by failure to suppress, rebound, and confirmed failure. Adherence in this cohort, as best as can be measured, was generally good as reflected by virological suppression and comparably low rates of loss to follow-up between groups. Thus, it seems unlikely that differences in adherence account for the differences that we found in virological outcomes.

The study has a number of limitations. First, although we demonstrated inferior virological outcomes in patients starting ART with prevalent tuberculosis and nevirapine, we were unable to demonstrate differences in survival or CD4 cell count change. Interpretation is therefore based on the premise that virological failure would eventually result in clinical failure. Second, although we believe that the decision to use nevirapine with rifampicin in this study has been a systematic one rather than by clinical indication, as an observational study, there remains the possibility of residual confounding by indication. In comparing the clinical characteristics of patients with tuberculosis when starting ART, it would appear that if anything, the sicker coinfected patients with a higher risk of virological failure were more likely to start efavirenz-based ART as evidenced by a lower median baseline CD4 cell count, a higher probability of having AIDS, and a shorter duration of tuberculosis treatment. Third, the detection limit of the viral load assay in our study was 400 copies/mL, whereas virological suppression to values 10-fold lower than this are required for long-term suppression.[32] Finally, it was not possible with the available data to compare tuberculosis outcomes between the groups studied.

Additional Findings

The association with increased weight and failure to suppress viral load in the combined model underlines the importance of weight in assessing the adequacy of NNRTI dosing. In addition to concerns about subtherapeutic dosing, at the other end of the spectrum, a low baseline weight has been associated with NNRTI toxicity.[19] More detailed analyses of associations between weight and virological outcomes and toxicity in patients on NNRTIs are required in this setting.

For both NNRTIs, CD4 cell count increases were higher in patients who commenced ART with prevalent tuberculosis compared with patients without tuberculosis. The likely explanation for this is the additive effect of the CD4 cell count increase observed when tuberculosis is treated in the absence of ART.[33] This confounds any attempt to determine the effect of the observed differences in virological outcomes on CD4 cell count changes.

The association between nevirapine use and failure to suppress viral load in patients without concurrent tuberculosis is consistent with data from both randomized controlled trials[18] and a number of observational studies.[34-36] The more rapid development of treatment-limiting toxicity in patients receiving nevirapine compared with those receiving efavirenz, irrespective of tuberculosis treatment, has previously been described together with a characterization of the toxicities involved.[19]

CONCLUSION

Nonnucleoside reverse transcriptase inhibitor–based ART is tolerable and effective when coadministered with rifampicin-containing antitubercular therapy. Probabilities of elevated viral loads during follow-up and confirmed virological failure are higher in patients with prevalent tuberculosis starting nevirapine-based ART. Given the continued reliance on nevirapine-containing ART regimens in Africa, together with the important role tuberculosis services play as an entry point for ART, further prospective studies exploring this outcome are warranted. One of the most striking aspects of our study was the demonstration that 40% of patients starting ART in recent years have concurrent tuberculosis, underscoring the public health importance of improving affordable treatment options for patients infected with HIV and tuberculosis in this setting.

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Author Contributions: Dr Boulle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Boulle, Van Cutsem, Cohen, Hilderbrand, Goemaere, Coetzee, Maartens.
Acquisition of data: Boulle, Van Cutsem, Hilderbrand, Mathee, Abrahams, Goemaere, Coetzee.
Analysis and interpretation of data: Boulle, Van Cutsem, Cohen.
Drafting of the manuscript: Boulle, Van Cutsem, Abrahams, Maartens.
Critical revision of the manuscript for important intellectual content: Van Cutsem, Cohen, Hilderbrand, Mathee, Goemaere, Coetzee.
Statistical analysis: Boulle, Van Cutsem, Cohen.
Obtained funding: Hilderbrand, Goemaere, Coetzee.
Administrative, technical, or material support: Van Cutsem, Hilderbrand, Mathee, Abrahams, Goemaere.
Study supervision: Van Cutsem, Coetzee, Maartens.
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Role of the Sponsor: None of these organizations were involved in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.
Previous Presentation: This study was presented in part at the 38th Union World Conference on Lung Health; November 8-12, 2007; Cape Town, South Africa.
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Exploring HIV risk perception and behaviour in the context of antiretroviral treatment: results from a township household survey

Paper overview and background

When the Khayelitsha project first started, universal access to ART in South Africa and other African countries was considered very unlikely. ART was therefore perceived as a valuable component of a comprehensive response to HIV spanning treatment and prevention, and that it would in part catalyse the entire response. This study was conceived to try and explore the impact of the availability of ART in Khayelitsha on behavioural risk factors in the broader Khayelitsha community.

Contribution to the thesis and novelty

This study is included in this thesis as the household survey provides a detailed description of the population in which the Khayelitsha ART intervention was being delivered (fifth objective). This assists with reflections on the generalisability of the ART programme findings. The study also addresses the fourth objective, which is to explore the effect of ART availability on HIV risk behaviour in the community, a distal outcome domain seldom measured in clinical studies.

Contributions of candidate

The study design and survey instrument were designed jointly by the Infectious Disease Epidemiology Unit at the University of Cape Town, and the Institute of Tropical Medicine in Antwerp, Belgium (Hilderbrand, Coetzee, Matthys, Boelaert). The candidate was responsible for the sampling of enumerator areas as well as individual households, for setting up and co-managing the data capture and quality control, and for the initial analysis of the survey.

The tables included in the published paper were produced by Joris Menten, a statistician in Antwerp. It was agreed that he would assist with the analysis as part of the Institute of Tropical Medicine / University of Cape Town collaboration on the project. The candidate had already conducted the entire analysis in Stata™ using the

built in survey commands provided by the software which account for the two-stage survey design. The candidate liaised closely with the statistician who was working in SAS™ and used a modelling approach to accommodate the study design, and ensured that the final analysis was consistent with the prior analysis in Stata™.

The candidate was primarily responsible for the drafting of all versions of the manuscript, which included integrating comments from co-authors.

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Exploring HIV risk perception and behaviour in the context of antiretroviral treatment: results from a township household survey

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The objective of this cross-sectional household survey was to assess factors influencing HIV risk perception, behaviour and intervention uptake in a community characterised by high HIV prevalence and availability of antiretroviral therapy (ART). The survey was conducted in Khayelitsha, South Africa and involved two-stage sampling with self-weighting clusters and random selection of households within clusters. One man and woman between 14 and 49 years old was interviewed in each household; 696 men and 879 women were interviewed for a response rate of 84% and 92% respectively. Ninety-three percent and 94% were sexually active with median age of sexual debut 15.3 and 16.5 years. Eighty-three percent and 82% reported a partner at the time of interview and 29% and 8% had additional partner(s). Forty-one percent and 33% reported condom use during the last sexual encounter. Thirty-seven percent of men not using condoms did not as they believed their partner to be faithful, whilst 27% of women did not as their partner refused. Twenty-eight percent and 53% had been tested for HIV. Having undergone HIV testing was not associated with condom usage, whilst current relationship status was the strongest association with condom usage for both men and women. In spite of a relatively high uptake of condoms and testing as well as ART availability, the HIV epidemic has continued unabated in Khayelitsha. Even greater coverage of preventive interventions is required, together with a national social and political environment that builds on the availability of both preventive and treatment services.

Keywords: HIV; sexual behaviour; South Africa; survey, prevention; treatment; anti retroviral therapy; condoms; voluntary counselling and testing

Introduction

The moral, social and economic imperative of providing antiretroviral treatment (ART) for people living with AIDS in resource-poor settings is today no longer questioned. However, the duality between prevention and treatment continues. In rich countries, prevention and treatment programmes are independently funded. Treating a patient with advanced AIDS is not put in balance with resource allocation for prevention, as is often the discourse in poorer countries (Marseille, Hofmann, & Kahn, 2002) where a false dichotomy between treatment and prevention is created. Such dichotomies can be detrimental to policy development for both prevention and care, whilst increasingly it is argued that these should be mutually reinforcing (Berkman, 2001; Coetzee et al., 2004; De Cock & Grubb, 2006; Salomon et al., 2005). Proponents of ART have argued that turning AIDS from a death sentence into a treatable chronic disease will alleviate the surrounding stigma and that breaking the silence results in a more open approach to prevention (Médecins sans Frontières & University of Cape Town, 2003).

In South Africa, numerous surveys have shown that the majority of people interviewed are aware of HIV, know its sexual transmission route and the protective benefits of using condoms (Johnson & Budlender, 2002; Kelly & Parker, 2000; Pettifor et al., 2005b; Shisana & Simbayi, 2002). This knowledge has not, however, translated into a marked reduction in new HIV infections; on the contrary national antenatal HIV prevalence has risen in South Africa from less than 1% in 1990 to 30% within 5 years (Department of Health, 2005). The aim of this survey was to assess HIV risk perception and risk behaviour in a specific context characterised by high HIV prevalence and exposure to treatment interventions, and to explore at a community level any association between the uptake of preventive interventions and the awareness of ART.

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Setting

Khayelitsha is a township on the outskirts of Cape Town, with a population of approximately 400,000 (Municipal Demarcation Board, 2007). The HIV seroprevalence in the two public-sector antenatal clinics in this district was 15% in 1999 and 33% in 2004 (Department of Health, 2005). Unemployment is high at 43%. Most residents rely on health services delivered by the state. In 1999, the first district-wide public-sector programme in South Africa to prevent the transmission of HIV from mother-to-child (PMTCT) was initiated in Khayelitsha (Abdullah, Young, Bitalo, Coetzee, & Myers, 2001). Dedicated clinics for adults and children with HIV were established in April 2000. In April 2001, the first patients were started on ART. By the end of the survey (March 2004), more than 1500 people were on ART in Khayelitsha, representing at that time one of the areas with the highest ART coverage. Other preventive interventions such as VCT, condom distribution, treatment of sexually transmitted infections and peer education have generally been available, although coverage of these interventions has never been systematically assessed.

Methods

Study design and sampling

The survey was conducted from September 2003 to March 2004 using a two-stage cluster design. The primary sampling units were enumerator areas (EA's) as defined for the national census, each consisting of around 200 households. Eighty out of a possible 622 clusters were selected on a probability proportional to size basis. Within each EA, 10 households were randomly sampled. In each household, one randomly selected man and woman aged between 14 and 49 years of age was interviewed. If eligible participants were not at home at the first visit, up to two repeat visits were made. The sample size was calculated based on previous surveys in Khayelitsha, which estimated condom use during last sexual intercourse at around 50% (Parker, Oyosi, Kelly, & Fox, 2002). Anticipating a design effect of 2, it was calculated that a sample of 800 men and 800 women between 14 and 49 years old would be required in order to provide a 95% confidence interval (CI) spanning 3% either side of this parameter for men and women separately.

Measurement

The questionnaire was developed based on prior qualitative work, the UNAIDS Best Practice Collection on Behaviour Monitoring and the questionnaire of a multi-centre study (Lagarde et al., 2001a), adapted and translated into isiXhosa and piloted in the community. The questionnaire is available on request.

Data management and statistical analysis

All the data were double entered and validated. Weighted proportions and means with 95%CI for patient characteristics, HIV/AIDS knowledge and sexual behaviour were estimated for men and women separately. Each cluster was weighted equally and CIs were calculated with cluster as primary sampling unit.

The associations between possible predictors and condom use or VCT were assessed using simple and multiple logistic regression models, adjusted for correlated outcomes at the cluster level using generalized estimating equations (GEE) (Hardin & Hilbe, 2003). The relationship between age and condom use or VCT was modelled using a piecewise linear effect.

Ethical approval for the study was obtained from the ethical committees of the University of Cape Town, South Africa and the Institute of Tropical Medicine in Antwerp, Belgium.

Results

Community characteristics

A total of 1576 people were interviewed, of whom 879 (55%) were women (Table 1). The response rate was 84% for men and 92% for women. The mean age of respondents was 28.3 years in men and 28.7 in women. A total of 1127 households were visited, with a mean of 3.0 adults and 1.1 children under 14 years. Two-thirds were informal structures. Although only 5% of respondents were born in Khayelitsha, more than half had been residing in Khayelitsha for 10 years or longer.

The literacy rate (defined as being able to read a newspaper in isiXhosa) exceeded 90% and was higher for women (98%) than for men (90%). Overall, 28% of men and 29% of women had obtained a school leaving certificate. Women were more likely to report being unemployed (45% versus 28%) and of those women who had some employment, they were less likely than men to be in full-time employment (17/34% compared to 33/51%). This is corroborated by a higher proportion of women relying on others for income. More women however were able to access social grants as a source of income (16% versus 2%).

In response to a question on circumcision, 75% of all male respondents reported having been circumcised; the median age of circumcision was 21 years.

Table 1. Sociodemographic characteristics and relationships of 14–49-year-old men and women in Khayelitsha (South Africa), 2003–2004.

	Men ($n=697$)		Women ($n=879$)	
	Estimate[†]	95%CI[†]	Estimate[†]	95%CI[†]
Age (mean)	28.3	(27.5–29.1)	28.7	(28.1–29.4)
Housing type (% living in brick house)	32.6	(25.2–40.9)	34.0	(26.7–42.2)
Schooling (%)				
No schooling	2.4	(1.5–3.9)	1.0	(0.5–1.9)
Primary school only	20.8	(17.2–25.0)	15.5	(12.9–18.6)
Secondary school below grade 10	23.5	(20.4–26.9)	20.1	(17.4–23.2)
Grade 10	25.6	(22.6–28.9)	34.3	(31.1–37.7)
Matric (school leaving)	26.0	(22.4–29.9)	25.1	(21.9–28.5)
Tertiary	1.6	(1.0–2.7)	4.0	(2.6–5.9)
Literacy (literate)	90.4	(87.6–92.6)	97.7	(96.3–98.6)
Place of birth (%)				
Khayelitsha	5.3	(3.8–7.5)	4.8	(3.5–6.6)
Cape Town	12.3	(9.4–16.1)	14.7	(11.5–18.5)
Western Cape	4.8	(3.3–7.0)	3.1	(2.0–4.8)
Eastern Cape	77.3	(72.2–81.8)	77.4	(73.0–81.3)
Other	0.2	(0.0–1.3)	0	
Time lived in Khayelitsha (%)				
Less than 1 year	7.3	(5.6–9.3)	5.6	(4.3–7.3)
1–5 years	18.9	(15.9–22.3)	18.9	(16.0–22.1)
5–10 years	22.3	(19.2–25.9)	25.0	(22.1–28.1)
More than 10 years	51.5	(47.7–55.4)	50.4	(47.0–53.9)
Employment status (%)				
Full-time employed	33.3	(29.4–37.4)	17.1	(14.3–20.2)
Irregular employment	13.5	(11.2–16.3)	9.1	(7.3–11.4)
Self-employed or informal sector	3.9	(2.6–5.7)	7.9	(6.0–10.3)
Unemployed and job-seeking	27.8	(24.2–31.7)	44.9	(41.1–48.6)
Student	20.9	(17.8–24.2)	18.1	(15.5–21.1)
Other	0.6	(0.3–1.4)	3.0	(2.0– 4.3)
Income source (%)				
Family and friends	46.7	(42.5–51.0)	63.8	(60.5–67.0)
Employment	51.8	(47.4–56.2)	30.8	(27.4–34.5)
Grant	2.3	(1.4–3.7)	15.5	(13.4–18.0)
Other or none	2.8	(1.8–4.4)	5.7	(4.2–7.6)
Circumcised (%)	74.9	(71.1–78.4)		

[†]Weighted mean or proportion adjusted for cluster as primary sampling unit. CI: Confidence interval.

Risk factors for HIV

In all 93% of men and 94% of women had ever been sexually active (Table 2), with an average age of sexual debut of 15.3 and 16.5 years. The total number of lifetime sexual partners reported was most frequently 5–10 for men and between 2–4 for women. In every age group men reported more lifetime sexual partners than women.

Men reported that their current partner was on average 4.4 years younger than them, accentuated when looking at men above 40 who reported partners seven years younger on average, whilst women of all ages reported partners who were 5.1 years older on average.

Of the 83% of men and 82% of women who reported a current sexual relationship at the time of the interview, 29% and 8% stated they had been sexually involved with someone outside of their regular relationship in the previous 12 months. Of these, men were more likely than women to have more than one additional partner.

Table 2. Sexual risk factors for HIV/AIDS of 14–49-year-old men and women in Khayelitsha (South Africa), 2003–2004.

	Men ($n=697$)		Women ($n=879$)	
	Estimate[†]	95%CI[†]	Estimate[†]	95%CI[†]
Sexually active (%)	92.6	(90.4–94.4)	94.0	(92.4–95.2)
Age at sexual debut (mean)	15.3	(14.9–15.7)	16.5	(16.2–16.8)
Relationships (%)				
Not in relationship	17.3	(14.7–20.1)	18.2	(15.7–20.9)
In relationship, but partner not living in Khayelitsha	13.5	(11.0–16.4)	14.0	(11.8–16.6)
In relationship, with partner in Khayelitsha	37.9	(33.9–42.0)	29.8	(27.1–32.7)
Living together with partner	31.4	(27.5–35.5)	38.0	(34.4–41.8)
Age difference with partner[‡] (mean)	4.4	(4.1–4.9)	−5.1	(−5.5– −4.7)
Used a condom last time with partner[‡] (%)	43.7	(39.0–48.4)	34.2	(30.1–38.5)
Generally use condom with partner[‡] (%)				
Never	46.2	(41.3–51.2)	51.5	(47.3–55.6)
Sometimes	22.4	(18.2–27.2)	22.5	(19.3–26.0)
Always	31.4	(27.1–36.1)	26.1	(22.3–30.2)
Lifetime number of sexual partners (%)				
None	7.8	(6.0–10.3)	6.3	(5.0–7.9)
1	3.4	(2.1–5.5)	14.7	(12.0–17.7)
2–4	26.9	(23.5–30.6)	58.4	(55.3–61.5)
5–9	28.5	(25.1–32.2)	16.4	(14.0–19.0)
10–19	20.2	(17.1–23.7)	3.9	(2.8–5.4)
20 or more	13.2	(10.6–16.3)	0.3	(0.1–1.0)
Number of sex partners apart from regular partner during the last 12 months[‡] (%)				
None	71.1	(67.2–74.8)	91.7	(89.6–93.3)
1	16.1	(13.2–19.4)	7.5	(6.0–9.3)
2–4	10.9	(8.8–13.4)	0.8	(0.3–2.1)
5–9	1.6	(0.8–3.1)	0	
10 or more	0.3	(0.1–1.2)	0	

[†]Weighted mean or proportion adjusted for cluster as primary sampling unit; CI: Confidence interval.
[‡]For those with regular sexual partner.

Knowledge about and exposure to HIV

The majority of respondents cited sexual and blood transmission as the modes of transmission for HIV (Table 3). Almost half of women identified vertical perinatal transmission. The majority of respondents spontaneously identified condoms as a means of preventing HIV infection.

Over half the respondents knew someone with HIV (54% of men and 63% of women), with women more likely to report knowledge of a family member infected than men (19% versus 10%) and similarly more likely to report having cared for someone with HIV. Close to three-quarters knew someone who had died due to HIV (73% and 76%).

Weight loss (79% & 74%), diarrhoea (29% & 31%), immobility (29% & 21%), hair loss (44% & 30%) and lesions on the lips (36% & 20%) were the symptoms and signs respondents most commonly identified with HIV. Twenty-two percent of men and 14% of women felt one could tell if someone had HIV by looking at them.

Condom use

When asked whether a condom was used the last time they had sex with any partner, 41% of men and 33% of women responded that they had (Table 4a). This was highest in the youngest age group with 68% of boys and 56% of girls reporting they used a condom at last intercourse.

Protection against HIV and other infections were the main reasons given by respondents for using condoms. There were large gender differences however in the reasons given for not using condoms: 37% of men felt they did not need to use condoms since "their partner is faithful" (compared to 23% of women), whereas 27% of women reported not using condoms as their partner refused (compared to 3% of men), rising to 72% when limited to those women

Table 3. Knowledge about HIV/AIDS transmission and prevention in 14–49 year-old men and women in Khayelitsha, 2003–2004.

	Men ($n=697$)		Women ($n=879$)	
	%[†]	95%CI[†]	%[†]	95%CI[†]
Knows someone with HIV	54.0	(49.5–58.5)	62.7	(59.1–66.2)
Knows of infected family members	9.7	(7.6–12.1)	18.5	(15.9–21.4)
Knows of infected friends/colleagues	14.7	(11.8–18.3)	27.6	(24.3–31.1)
Cared for someone with HIV	6.0	(4.1–8.6)	15.0	(12.6–17.9)
Knows someone who died from HIV	72.7	(68.8–76.4)	76.0	(72.8–78.9)
Knows of a family member who died from HIV	12.4	(9.9–15.4)	22.9	(20.3–25.6)
Reported modes of contracting HIV[‡]				
Unprotected sex	95.3	(93.5–96.7)	94.7	(93.0–96.0)
Blood contact	81.4	(78.2–84.3)	84.4	(81.7–86.9)
MTCT	11.1	(8.6–14.1)	49.5	(44.9–54.0)
Dirty needles	23.5	(20.0–27.4)	60.2	(54.9–65.1)
Razorblades	22.4	(19.5–25.6)	52.7	(47.6–57.8)
Toothbrush	15.5	(12.8–18.6)	49.0	(44.3–53.6)
Punishment	0.6	(0.3–1.5)	25.5	(21.6–29.7)
Foreigners	5.7	(4.2–7.8)	32.6	(28.7–36.9)
Reported ways of preventing HIV[‡]				
Condoms	90.1	(87.2–92.5)	97.3	(95.9–98.1)
Abstinence	35.0	(31.6–38.6)	38.2	(34.6–42.0)
Being faithful	39.2	(35.4–43.3)	23.2	(20.3–26.3)
PMTCT	3.3	(2.0– 5.3)	18.9	(16.1–22.0)
Behaving properly	14.0	(10.9–17.9)	21.0	(17.7–24.7)
Believes one can visually tell if someone is HIV-infected	21.9	(18.6–25.6)	14.4	(12.0–17.2)
Reported symptoms/signs of HIV/AIDS[‡]				
Weight loss	79.2	(75.8–82.2)	73.6	(69.5–77.3)
Diarrhoea	28.6	(24.9–32.7)	31.3	(28.1–34.7)
Inability to walk	29.0	(25.9–32.4)	21.1	(18.5–24.0)
Hair loss	44.2	(39.6–48.9)	30.4	(27.4–33.7)
Red lips	36.2	(32.2–40.4)	20.3	(17.4–23.5)

[†] Weighted proportion adjusted for cluster as primary sampling unit; CI: Confidence interval.
[‡] All answers occurring in at least approximately 20% of respondents for either gender.

who had wanted to use a condom in their most recent sexual encounter but did not. Less than one in ten respondents (7% of men and 10% of women) reported buying condoms.

Models to explore associations with condom use confirmed that condom use was highest in the youngest age groups and decreased with increasing age until age 35 in men and 25 in women (Table 4b). Condom use was higher for respondents with at least some secondary school education (OR: 1.3 and 1.9 in men and women respectively). The lowest condom use was seen in couples living together and highest in short-term relationships. For men, condom use was higher among those who knew how HIV is transmitted (OR: 1.8), who knew that condom use and abstinence prevent HIV infection (OR: 10.3 and 1.5) and among those who discuss HIV/AIDS with friends (OR: 1.7). For women, condom use was negatively associated with living in a one-roomed house (OR: 0.6) but higher in those who knew someone who had died of AIDS (OR: 1.7), in those who discussed HIV/AIDS with others (OR: 1.6) and in those with specific knowledge of ART and the need for treatment to be taken life-long (OR: 2.1).

Voluntary counselling and testing

Over three-quarters (78%) of men and almost all (97%) women said they knew where they could be tested for HIV and 28% of men and 53% of women reported having been tested (Table 5a). When respondents who had tested were asked whether they would feel comfortable disclosing their HIV status to the interviewer, the minority were uncomfortable

Table 4a. Condom use in 14–49 year-old, sexually active men and women in Khayelitsha (South Africa), 2003–2004.

	Men ($n=648$)		Women ($n=823$)	
	%†	95%CI†	%†	95%CI†
Condom use in any last sexual contact	40.7	(36.4–45.1)	32.6	(28.9–36.5)
In 14–19 year-old respondents	67.6	(53.4–79.1)	56.7	(44.8–67.9)
In 20–29 year-old respondents	51.6	(45.1–58.1)	35.7	(29.9–42.0)
In 30–39 year-old respondents	25.9	(19.9–32.9)	27.8	(22.0–34.4)
In 40–49 year-old respondents	21.0	(14.0–30.5)	20.6	(14.6–28.2)
Reason for condom use‡				
To protect myself against HIV	49.3	(45.1–53.5)	32.8	(29.7–36.0)
To protect my partner against HIV	21.1	(18.0–24.6)	9.1	(7.1–11.7)
To protect against STI's	35.7	(32.0–39.7)	32.3	(28.8–36.0)
To prevent pregnancy	20.3	(17.3–23.5)	22.2	(18.8–26.0)
Reason for not using condoms‡				
Don't enjoy sex with them	13.6	(11.3–16.2)	1.0	(0.5 –1.9)
Partner is faithful	37.2	(32.9–41.8)	23.2	(19.6–27.2)
Partner refuses	2.5	(1.5 –4.2)	27.2	(24.0–30.6)
Buys condoms	7.3	(5.1–10.4)	9.8	(7.2–13.3)
Place for getting condoms for free‡				
Public sector clinic	52.5	(48.3–56.6)	46.2	(42.2–50.3)
Ever wanted to but did not use condoms	18.4	(15.0–22.3)	28.8	(25.5–32.4)
Reasons for not using condoms‡,*				
None available	15.0	(10.5–21.1)	7.7	(5.1–11.4)
Alcohol	18.3	(13.8–23.8)	0.8	(0.2–3.0)
Partner refused	14.8	(10.1–21.2)	72.1	(65.6–77.8)

† Weighted proportion adjusted for cluster as primary sampling unit; CI: Confidence interval.
‡ All answers occurring in at least 10% of respondents for either gender.
* Responses to this question are based on 105 men and 224 women who answered the preceding question in the affirmative.

disclosing (4% of men and 1% of women). Of note, only 1% of men and 6% of women who had tested reported testing HIV-positive.

Models restricted to sexually active individuals demonstrated a number of associations with having tested for HIV (Table 5b). The strongest associations in men were a partner (OR: 9.6) or other acquaintance (OR: 3.3) having tested for HIV, increasing age until 30 (OR: 1.2/year), being full-time employed (all other categories negatively associated), being in a relationship but not living with their partner, having a partner less than five years younger (OR = 0.52 if greater) and knowing that condoms prevent HIV infection (OR: 2.3). In women, increasing age above 30 was negatively associated with VCT (OR: 0.9/yr), whilst not working or job-seeking (OR: 3.8), being born somewhere other than the Eastern Cape, having older partners (OR: 1.6), openness about HIV (OR: 1.9), having cared for someone with HIV (OR: 2.1), a partner having tested (OR: 2.5) and knowing that condoms prevent HIV (OR: 2.6) were positively associated with VCT. In addition, knowledge about PMTCT (OR: 4.2) and knowing people on ART (OR: 2.6) were strongly associated with having tested.

Knowledge of prevention and treatment interventions

Overall, 8% of men and 7% of women believed that HIV could be cured (Table 5a). More women than men had heard of ART (43 versus 27%).

For all ages combined, radio was the most common sources of information on ART, followed by television. Four respondents were themselves on ART, whilst 23% of men and 36% of women knew of the Treatment Action Campaign, the most prominent organisation in the area advocating for treatment.

Discussion

Khayelitsha is characterised by extremely high levels of HIV sero-prevalence mirroring that in South Africa more generally. Living in Khayelitsha reflects many of the challenges faced by the urban poor, who are generally considered to be at higher risk of HIV infection for a myriad of reasons. Khayelitsha is a community that has been at the forefront of activism

Table 4b. Multiple logistic regression model for association with condom use during last sexual contact in 14–49-year-old, sexually active men and women in Khayelitsha (South Africa), 2003–2004.

Men				
Factor	Category	OR†	95%CI†	*P*-value†
Age	Slope (OR/yr) for <35 years	0.96	(0.92–0.99)	0.025
	Slope (OR/yr) for ≥ 35 years	1.04	(0.96–1.13)	0.310
Type of relationship	Not in relationship	2.31	(1.20–4.46)	< 0.001
	In relationship, but partner not living in Khayelitsha	4.29	(2.29–8.07)	
	In relationship of <1 yr, with partner in Khayelitsha	9.48	(4.64–19.34)	
	In relationship of ≥ 1 yr, with partner in Khayelitsha	6.14	(3.41–11.04)	
	Living together with partner	Reference category		
Education	Secondary school or better	1.33	(0.81–2.18)	0.260
Knowledge route of transmission				
	Quotes 2 correct items	1.76	(1.13–2.74)	0.012
Knows that condoms prevent HIV transmission				
	Yes	10.28	(3.45–30.63)	< 0.001
Knows that abstinence prevents HIV transmission				
	Yes	1.50	(1.00–2.24)	0.048
Talks about HIV/AIDS				
	With friends	1.68	(1.03–2.76)	0.038
Women				
Age	Slope (OR/yr) for <25 years	0.89	(0.83–0.96)	0.005
	Slope (OR/yr) for ≥ 25 years	1.00	(0.97–1.03)	0.835
Type of relationship	Not in relationship	2.54	(1.47–4.37)	< 0.001
	In relationship, but partner not living in Khayelitsha	3.82	(2.27–6.43)	
	In relationship of <1 yr, with partner in Khayelitsha	7.19	(3.83–13.52)	
	In relationship of ≥ 1 yr, with partner in Khayelitsha	2.77	(1.78–4.32)	
	Living together with partner	Reference category		
Education	Secondary school or better	1.93	(1.20–3.12)	0.007
Housing type	One room house	0.55	(0.32–0.94)	0.029
Knows somebody who died of AIDS				
	Yes	1.67	(1.08–2.59)	0.022
Talks about HIV/AIDS				
	With friends, family or partner	1.60	(0.94–2.74)	0.086‡
Knowledge of ART	Knows ART needs to be taken for ever	2.09	(1.24–3.53)	0.042
	Knows ART but not that it needs to be taken for ever	1.17	(0.79–1.74)	
	Has not heard of ART	Reference category		

† Adjusted odds-ratio's (OR), 95% confidence interval (CI) and *p*-values from multiple logistic regression model.

around accessing antiretroviral treatment and is looked to for evidence of the synergies between treatment and prevention interventions. This survey demonstrates that many of the best practice prevention interventions do in fact have a high uptake in Khayelitsha. There are relatively high levels of VCT uptake, condoms use is consistent with or higher than in other surveys (Pettifor et al., 2005b; Shisana & Simbayi, 2002) and knowledge about HIV appears to be good.

At the same time however, HIV prevalence has continued to rise unabated, including in the youngest age groups (Department of Health, 2005). A particular conglomeration of risk factors that are common to the epidemic in the region continue in Khayelitsha, including early sexual debut, missed opportunities for condom usage, concurrent relationships, especially amongst men where they are frequently multiple, age differentials between male and female partners, and the inability of women to negotiate condom usage when they would otherwise choose to use condoms. These estimates are not dissimilar to those described in other South African surveys (Parker et al., 2002; Pettifor et al., 2005a; Pettifor et al., 2005b; Shisana &

Table 5a. Uptake of VCT and knowledge of interventions in 14–49-year-old men and women in Khayelitsha (South Africa), 2003–2004.

	Men ($n=697$)		Women ($n=879$)	
	%†	95%CI†	%†	95%CI†
Know where one can be tested for HIV	77.9	(74.4–81.1)	96.5	(95.1–97.5)
Ever tested for HIV	28.0	(25.1–31.1)	53.3	(49.1–57.5)
In 14–19 year-old respondents	5.7	(2.8–11.5)	24.1	(17.3–32.6)
In 20–29 year-old respondents	28.9	(23.7–34.7)	61.9	(55.6–67.7)
In 30–39 year-old respondents	42.3	(34.5–50.5)	62.5	(56.0–68.5)
In 40–49 year-old respondents	27.8	(19.1–38.7)	41.5	(32.8–50.7)
HIV status‡				
Preferred not to disclose	4.1	(2.0–8.1)	0.8	(0.3– 2.3)
HIV-positive	1.1	(0.3–4.4)	6.1	(4.3–8.5)
HIV-negative	94.8	(90.5–97.2)	93.1	(90.6–95.1)
Reason for testing‡				
Told by health staff	7.9	(4.2–14.6)	11.4	(8.5–15.2)
MTCT	2.3	(0.9–6.0)	44.9	(40.1–49.7)
Was sick	25.4	(19.5–32.4)	18.2	(14.4–22.7)
Wanted to know status	51.2	(43.0–59.3)	39.3	(34.8–44.0)
Reason for not testing¥				
I am afraid of the result	28.5	(24.2–33.3)	49.1	(43.7–54.4)
I do not feel at risk	31.9	(27.0–37.3)	27.1	(22.8–31.9)
I am not sexually active	14.3	(11.4–17.7)	13.4	(10.6–17.0)
I do not know where to test	18.7	(15.3–22.6)	3.1	(1.7–5.5)
Knows someone who had tested	47.2	(43.3–51.1)	48.9	(45.2–52.7)
Talks about HIV with friends	82.3	(79.4–84.8)	74.3	(71.1–77.4)
Talks about HIV with partner	75.1	(71.7–78.3)	77.0	(73.9–79.7)
Talks about HIV with other relatives	55.9	(51.6–60.1)	52.1	(48.8–55.4)
Heard of the Treatment Action Campaign	22.8	(19.7–26.2)	36.5	(33.2–39.9)
Believes HIV can be cured	8.1	(5.9–11.2)	6.7	(5.0– 8.9)
Knows that TB can be cured	97.5	(95.8–98.5)	97.2	(95.7–98.2)
Heard of ART	26.9	(23.6–30.5)	43.3	(39.2–47.6)
Knows someone on ART¶	14.1	(9.2–21.1)	21.6	(17.2–26.9)
Knows where to get ART¶	68.9	(60.9–75.9)	73.4	(68.9–77.5)
Source of information on ART¶				
Newspaper	23.3	(17.8–29.9)	8.1	(5.6–11.5)
Radio	61.1	(52.0–69.4)	42.1	(36.9–47.5)
Church	0.6	(0.1–2.3)	0.4	(0.1–1.8)
Television	50.3	(42.7–58.0)	41.3	(35.6–47.1)
School	5.0	(2.7–8.9)	7.6	(5.2–11.0)
Treatment Action Campaign	4.8	(2.1–10.4)	5.6	(3.7–8.4)
Clinic	10.9	(6.9–16.8)	31.9	(26.8–37.4)
Other	8.2	(4.4–14.9)	13.6	(10.3–17.8)

† Weighted proportion adjusted for cluster as primary sampling unit; CI: Confidence interval. ART: antiretroviral therapy; PMTCT: Prevention of mother-to-child transmission of HIV.
‡ For those who tested.
¥ For those who did not test.
¶ For those who have heard of ARVs.

Simbayi, 2002; South African Department of Health, 2001).

Given the importance of consistency in condom use (Ahmed et al., 2001; Lagarde et al., 2001b), it is notable that nearly 20% of men and 30% of women would like to have used a condom the last time they had sex but did not, with lack of availability remaining an important contributing cause

The age differential between male and female partners is particularly marked in Khayelisha, in

Table 5b. Multiple logistic regression model for association with VCT uptake in 14–49-year-old, sexually active men and women in Khayelitsha (South Africa), 2003–2004.

Men				
Factor	Category	OR†	95%CI†	*P*-value†
Age	Slope (OR/yr) for <30 years	1.17	(1.09–1.26)	<0.001
	Slope (OR/yr) for ≥30 years	0.97	(0.92–1.03)	0.318
Type of relationship	Not in relationship	1.10	(0.72–2.68)	0.081
	In relationship, but partner not living in Khayelitsha	1.39	(2.29–8.07)	
	In relationship of <1 yr, with partner in Khayelitsha	2.33	(1.10–4.94)	
	In relationship of ≥1 yr, with partner in Khayelitsha	2.14	(1.12–4.08)	
	Living together with partner	Reference category		
Education	Secondary school or better	1.20	(0.72–2.00)	0.497
Employment Status	Retired, disabled, homemaker	0.24	(0.06–1.04)	
	Unemployed and job-seeking	0.82	(0.49–1.40)	
	Irregular, self or informal employed	0.49	(0.29–0.84)	0.040
	Student	0.54	(0.23–1.27)	
	Full-time employed	Reference category		
Age difference with partner				
	Female partner >5 yrs younger	0.52	(0.32–0.83)	0.006
Knows someone who has tested				
	Yes, partner	9.57	(5.21–17.57)	< 0.001
	Yes, somebody other than partner	3.31	(2.13–5.14)	
	Knows nobody who has tested	Reference category		
Knows that condoms prevent HIV transmission				
	Yes	2.26	(1.12–4.55)	0.022
Women				
Age	Slope (OR/yr) for <30 years	1.03	(0.98–1.09)	0.188
	Slope (OR/yr) for ≥30 years	0.91	(0.88–0.95)	< 0.001
Type of relationship	Not in relationship	0.94	(0.56–1.57)	0.189
	In relationship, but partner not living in Khayelitsha	0.56	(0.33–0.96)	
	In relationship of <1 yr, with partner in Khayelitsha	0.49	(0.19–1.31)	
	In relationship of ≥ 1 yr, with partner in Khayelitsha	0.71	(0.45–1.12)	
	Living together with partner	Reference category		
Education	Secondary school or better	1.24	(0.78–1.98)	0.372
Employment status	At home, retired or disabled	3.80	(1.38–10.46)	< 0.001
	Unemployed and job seeking	1.72	(1.11–2.65)	
	Irregular, self or informal	1.12	(0.63–1.98)	
	Student	0.60	(0.32–1.14)	
	Full time employed	Reference category		
Place of birth	Born in Eastern-Cape	0.61	(0.40–0.94)	0.024
Age difference with partner				
	Male partner >5 yrs older	1.60	(1.12–2.28)	0.010
Has knowledge of ART	Knows somebody on ART	2.59	(1.36–4.94)	0.020
	Knows of ART, but no one on ART	1.30	(0.92–1.85)	
	Has not heard of ART	Reference category		
Knows someone who has tested				
	Yes, partner	2.52	(1.28–4.99)	0.008
	Yes, other than partner	0.86	(0.60–1.23)	
	Not knowing anyone who has tested	Reference category		
Has knowledge of PMTCT				
	Yes	4.16	(2.62–6.61)	< 0.001
Knows that condoms prevent HIV transmission				
	Yes	2.58	(1.12–5.93)	0.026

Table 5b (*Continued*)

Men				
Factor	Category	OR†	95%CI†	*P*-value†
Discusses HIV/AIDS	With friends, family or partner	1.92	(1.12–3.31)	0.018
Has cared for someone with HIV				
	Yes	2.11	(1.23–3.62)	0.007

† Adjusted odds-ratio's (OR), 95% confidence interval (CI) and *p*-values from multiple logistic regression model. ART: antiretroviral therapy; PMTCT: Prevention of mother-to-child transmission.

keeping with a number of studies in Southern Africa in which older male partners are postulated to place young women at greater risk of HIV acquisition (Glynn et al., 2001; Gregson et al., 2002; Laga, Schwartlander, Pisani, Sow, & Carael, 2001).

Given recent evidence on the potential role of circumcision in contributing to HIV prevention (Auvert, Taljaard, Lagarde, Sobngwi-Tambekou, Sitta, & Puren, 2005), the potential impact on the epidemic of an intervention around circumcision in this community would need to be considered in the light of the extremely high proportion of men who are for traditional reasons already circumcised in early adulthood, as well as the current age at circumcision.

In understanding the forces shaping risk behaviour, the importance of distal contextual factors in addition to personal factors is increasingly stressed (Eaton, Flisher, & Aaro, 2003; Mathews, 2005). In this study, an important negative finding was a lack of association with having undergone VCT and condom usage in the last sexual encounter, whereas trial evidence suggests an association between prior VCT and risk behaviour (Allen et al., 2003; Hogan & Salomon, 2005). In contrast, responses suggesting openness around HIV, knowledge of antiretroviral interventions and exposure to individuals on antiretroviral treatment were variously associated with condom usage and testing. The implausibly low proportions of patients who admit in the survey to being HIV-infected in spite of apparent openness, reflects however ongoing stigma associated with the diagnosis.

There are two broad conclusions from this study – firstly, modest increases in coverage of current best-practice prevention interventions are limited in the extent to which they can impact on a mature generalised epidemic as is found in Khayelitsha. In the same way as a constant expansion of the clinical service platform is required in order to meet treatment needs and approach universal access, so too is a constant, aggressive and sustained expansion in the promotion of prevention interventions required in order to attain even higher levels of coverage.

Secondly, the relationship between treatment and prevention services is impossible to unravel in the constantly changing context of a maturing HIV epidemic. Due to the global commitment to treatment access, it is fortunately no longer necessary to justify treatment interventions on the putative basis of their impact on prevention. Furthermore, discussions on the synergies between treatment and prevention often focus on personal and proximal issues. The high reliance on broadcast media as a source of information in this survey point to the importance of the distal context, where South Africa has lagged behind many other countries in the region in terms of the visibility, political commitment and priority afforded to both treatment and preventive interventions for HIV in the national discourse. It is at this level perhaps that the greatest synergies might exist between treatment and preventive paradigms.

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Antiretroviral therapy and early mortality in South Africa

Paper overview and background

The paper was initially entitled "Scaling-up of antiretroviral therapy is associated with good retention in care, and declining early mortality five years into a provincial programme", but was changed on request of editors of the journal where it was submitted. The paper describes a body of work that the candidate was involved in which ran in parallel to the Khayelitsha cohort, and incorporated the Khayelitsha data. The paper explores the outcomes throughout the entire province as ART availability extended and became widely available, and is based on the aggregate reporting system used by the provincial government.

Contribution to the thesis and novelty

This analysis addresses the final objective, which is to determine the scalability of ART within the Western Cape Province. The paper is unique in being able to report comprehensively on a routine government programme where the majority of monitoring has been entirely paper-based. The paper places a strong emphasis on describing and advocating for a basic monitoring system, but also demonstrates excellent outcomes at scale, improvements in immunological status at ART initiation over calendar time in concert with increased access to ART, and opposite temporal trends in mortality and loss to follow-up.

Contributions of candidate

The monitoring system on which this paper is based was developed under the leadership of the candidate through his service responsibilities to government as a public health registrar from 2002-2004, and on contract to government from 2005 onwards. The candidate was responsible for all analyses in the paper, and was primarily responsible for the drafting of all versions of the manuscript including the integration of comments from co-authors.

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Antiretroviral therapy and early mortality in South Africa

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Objective To describe province-wide outcomes and temporal trends of the Western Cape Province antiretroviral treatment (ART) programme 5 years since inception, and to demonstrate the utility of the WHO monitoring system for ART.
Methods The treatment programme started in 2001 through innovator sites. Rapid scaling-up of ART provision began early in 2004, located predominantly in primary-care facilities. Data on patients starting ART were prospectively captured into facility-based registers, from which monthly cross-sectional activity and quarterly cohort reports were aggregated. Retention in care, mortality, loss to follow-up and laboratory outcomes were calculated at 6-monthly durations on ART.
Findings By the end of March 2006, 16 234 patients were in care. The cohort analysis included 12 587 adults and 1709 children. Women accounted for 70% of adults enrolled. After 4 and 3 years on ART respectively, 72.0% of adults (95% confidence interval, CI: 68.0–75.6) and 81.5% (95% CI: 75.7–86.1) of children remained in care. The percentage of adults starting ART with CD4 counts less than 50 cells/μl fell from 51.3% in 2001 to 21.5% in 2005, while mortality at 6 months fell from 12.7% to 6.6%, offset in part by an increase in loss to follow-up (reaching 4.7% at 6 months in 2005). Over 85% of adults tested had viral loads below 400 copies/ml at 6-monthly durations until 4 years on ART.
Conclusion The location of care in primary-care sites in this programme was associated with good retention in care, while the scaling-up of ART provision was associated with reduced early mortality.

Bulletin of the World Health Organization 2008;86:678–687.

Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

The national antiretroviral treatment (ART) programme in South Africa was launched in April 2004.[1] However, for some years prior to this, demonstration projects had provided ART to HIV-infected individuals with advanced disease through government health services. Several projects were located in the Western Cape Province which, as a result, is able to report on outcomes up to 4 years after initiation of therapy. The first such project began providing ART in Khayelitsha in May 2001,[2,3] followed by a project in Gugulethu in September 2002.[4–6]

Since inception, the clinical guidelines and approaches to monitoring used in the Western Cape Province have been in line with those recommended by WHO.[7–9] The treatment setting is reflective of public sector health services in South Africa. A description of outcomes 5 years into this provincial programme, and after significant scaling-up of care, has relevance to what can be anticipated in South Africa and other similar settings in the region.

This paper demonstrates that robust and useful information can be generated using a basics-first, paper-based monitoring system, as recommended by WHO.[10] There are some sites in the province that collect clinical data electronically and enhance these data for cohort surveillance and research. These are designated as sentinel sites and address particular clinical and epidemiological questions. This takes pressure off the remaining sites from having to institute complex monitoring systems and ensures that in the majority of sites only the information essential for management and programme assessment is collected.

The aim of this paper is to describe the key clinical outcomes in the Western Cape provincial ART programme, in patients on therapy for up to 4 years, and the evolution of the programme over a 5-year period. Secondary aims are to demonstrate the field utility of the WHO monitoring guidelines and the feasibility of scaling-up services through primary-care sites.

Programme description

The first project to routinely offer ART in the public sector and on a district-wide basis in South Africa was started in 2001 as a partnership between the provincial government and Médecins Sans Frontières in the Cape Town township of Khayelitsha. At that time, several local clinicians had already been involved in ART provision through clinical studies and private funding and

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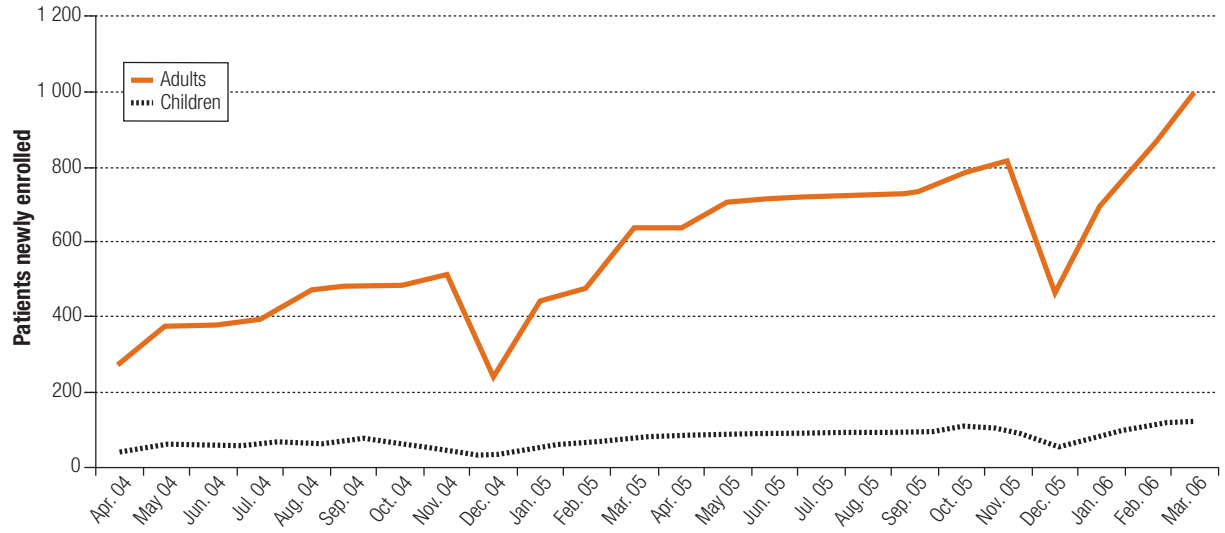
Fig. 1. **Trends in enrolment of patients on ART**

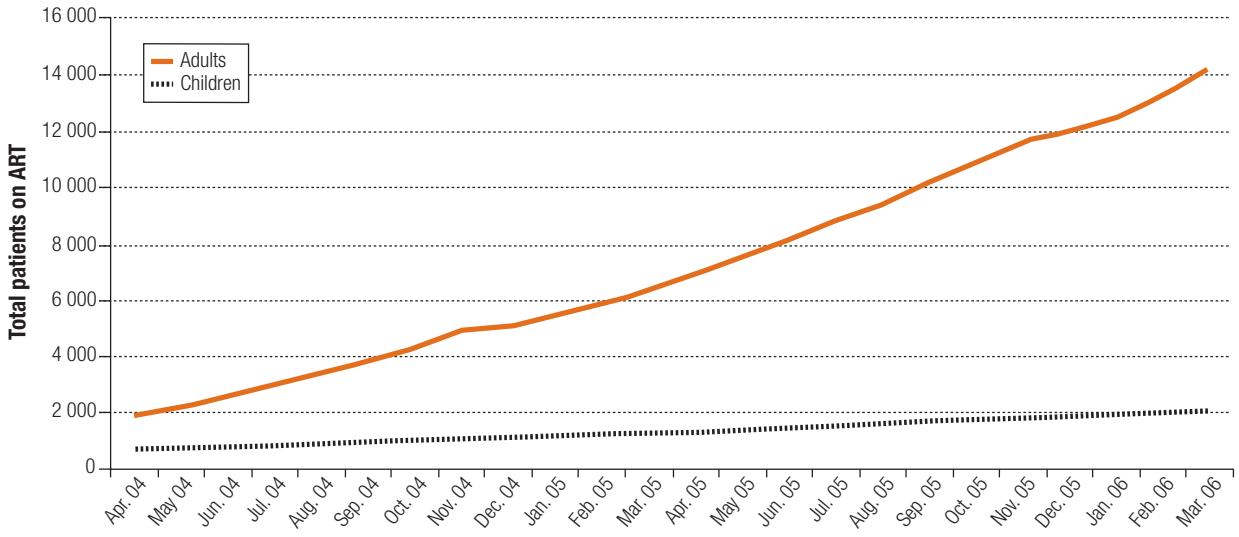


ART, antiretroviral therapy.

were able to support this and subsequent initiatives. These early sites can be considered as "innovator sites" in as far as they were able to grapple with many of the logistics of setting up services in anticipation of a more rapid scaling-up of ART services. By the time the national programme was launched in South Africa in April 2004, there were 16 discrete sites offering ART in the province, eight of which were in primary care. At this time there were 2327 patients receiving ART. By the end of March 2006, there were 16 234 patients receiving ART (87% adults) across 43 sites, the majority being treated in primary-care settings (67% in clinics and community health centres, and 13% in district hospitals). Enrolment increased steadily over this time to reach 1000 patients per month, with seasonal decreases in enrolment each December (Fig. 1 and Fig. 2). Care was first offered as part of the primary-care HIV intervention for children in 2002, with follow-up for children in this analysis extending to 3 years. Children were defined as patients starting ART under the age of 14 years.

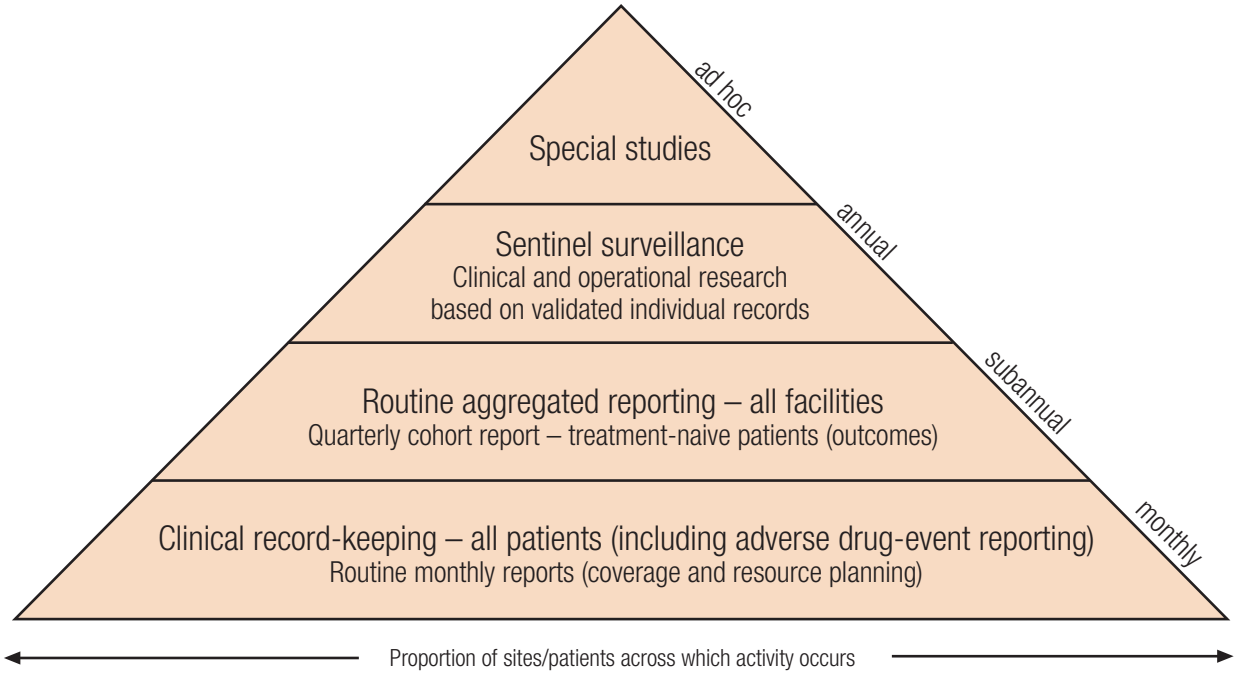
Patients were considered eligible for ART if they had a stage IV illness (excluding extrapulmonary tuberculosis) or a CD4 count less than 200 cells/μl. The adult regimens used throughout comprised two nucleotide reverse transcriptase inhibitors (NRTIs) and one non-nucleotide reverse transcriptase inhibitor (NNRTI). Initially, the NRTI backbone in Khayelitsha comprised zidovudine and lamivudine, but was later changed to stavudine and lamivudine in line with the national programme. Paediatric regimens varied, with NNRTIs and protease inhibitors

Fig. 2. **Trends in total patients on ART**



ART, antiretroviral therapy.

Fig. 3. **A tiered routine monitoring system for ART**



ART, antiretroviral therapy.

being variously used with the NRTI backbone.

Six-monthly CD4 counts and viral-load testing were provided in the programme, together with safety monitoring according to the specific regimens. The protocol for changing to second-line therapy was two consecutive viral loads above 5000 copies/ml.[7] All laboratory tests were conducted by the National Health Laboratory Services. CD4 counts were performed using the panLeucogating method.[11] Viral loads were conducted using the NucliSens HIV-1 QT® assay, and later NucliSens EasyQ® HIV-1 assay (bioMérieux, Boxtel, the Netherlands) for which the upper limit of detection is just under 400 copies/ml, hence the use of 400 copies/ml as the definition of suppression in all registers and analyses.

Data collection and analysis

The routine monitoring system

Data analysed were collected through the routine monitoring system. This system is one component of a framework for the monitoring of the ART programme in the province (Fig. 3). Other components include observational cohort studies in sentinel sites, special studies to address priority clinical research questions, and a passive-stimulated pharmacovigilance reporting system.

Patients are entered into a register in the order in which they start ART. Monthly reporting is universal across the sites and comprises cross-sectional patient and enrolment totals (Fig. 1 and Fig. 2), the essential information required by managers to keep track of resource allocation and progress against targets. Quarterly cohort reports are also universal and are provided a quarter in arrears to allow sites to complete the ascertainment of outcomes before reporting. These reports are aggregated by starting quarter, as well as by 6-monthly durations on ART, allowing for cohort outcomes to be reported. The metrics reported on quarterly include regimen (first- or second-line), CD4 count, viral load and outcome (i.e. in care, transferred out, lost to follow-up, died).

When aggregating from the registers, the measure of advanced immune suppression at baseline is determined by the proportion of adults with a baseline CD4 cell count of less than 50 cells/μl and in children a CD4 percentage of less than 15% of total lymphocytes. Immunological response during follow-up is determined by the proportion of patients tested with CD4 cell counts above 200 cells/μl or greater (20% in children) and virological response by the proportion of patients tested with viral loads below 400 copies/ml. All cohort analyses are limited to treatment-naive patients.

Data analysis

The monthly data are presented as cross-sectional monthly totals, whilst the quarterly data are presented as combined annual enrolment cohorts followed up until study closure. The monthly data cover April 2004 to March 2006, whilst the cohort data include patients enrolled between May 2001 and December 2005, followed until March 2006. Owing to the aggregate nature of the data, all data are presented as proportions with 95% binomial confidence intervals. The definition of "remaining in care" is patients who had had at least one visit in the preceding 90 days. Correspondingly, the definition of "loss to follow-up" is patients who had not had a contact with the health services for 90 days or more. The small number of patients who transferred their care to other sites are excluded in both the numerator and the denominator in the calculation of the proportions remaining in care, died and lost to follow-up. These measures

Table 1. **Estimates of retention in care for treatment-naive adults**

Duration on ART (months)	0	6	12	18	24	30	36	42	48
Total adults starting ART	12 587	8 341	4 726	2 167	852	561	328	189	80
Started before		30 Jun 2005	31 Dec 2004	30 Jun 2004	31 Dec 2003	30 Jun 2003	31 Dec 2002	30 Jun 2002	31 Dec 2001
Deaths since start[a,b]		545 (6.7)	397 (8.8)	239 (11.6)	131 (15.8)	96 (17.6)	60 (18.9)	36 (19.7)	18 (23.1)
Lost to follow-up since start[b,c]		340 (4.2)	286 (6.3)	148 (7.2)	27 (3.3)	18 (3.3)	13 (4.1)	5 (2.7)	1 (1.3)
Transfers out since start[b,d]		223 (2.7)	214 (4.5)	98 (4.5)	23 (2.7)	16 (2.9)	10 (3.0)	6 (3.2)	2 (2.5)
Remaining in care – absolute[e,f]		89.1 (88.4–89.8)	84.9 (83.8–85.9)	81.3 (79.5–83.0)	80.9 (78.1–83.6)	79.1 (75.4–82.4)	77.0 (72.0–81.6)	77.6 (70.9–83.4)	75.6 (64.6–84.7)
Remaining in care – cumulative[g,h]		89.5 (88.9–90.1)	85.3 (84.5–86.1)	82.1 (80.9–83.1)	80.0 (78.5–81.4)	77.8 (75.9–79.6)	74.8 (72.1–77.2)	73.2 (70.0–76.1)	72.0 (68.0–75.6)

ART, antiretroviral therapy.
[a] Deaths since start = deaths / (total - transfers out).
[b] Values in parentheses are percentages.
[c] Lost to follow-up since start = losses to follow-up / (total - transfers out).
[d] Transfers out since start = transfers out / total.
[e] Remaining in care – absolute = (total - losses to follow-up - deaths - transfers out) / (total - transfers out).
[f] Values in parentheses are exact binomial confidence intervals.
[g] Weighted Kaplan–Meier estimate.
[h] Values in parentheses are Greenwood point-wise confidence intervals.

are limited to those patients followed up for at least the full duration under analysis. In addition, the proportion of patients remaining in care is further described as Kaplan–Meier estimates based on weighted survival data derived from the count data. All analyses were performed using Stata statistical software version 9.0 (StataCorp. LP, College Station, TX, United States of America).

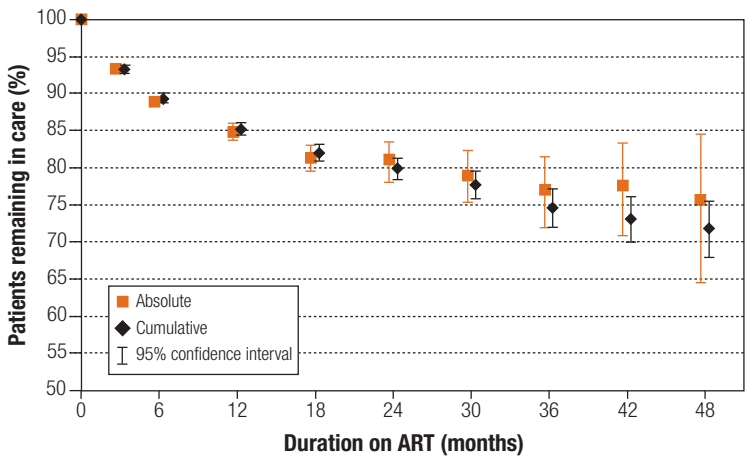
Results

Overall, 12 587 adults and 1709 children were included in this cohort report, totalling 14 296 treatment-naive patients. This is a near-complete representation of all public-sector patients started on ART in the Western Cape Province by the end of 2005. Follow-up for the oldest quarterly cohorts extends to 4 years on treatment. A further 2.4% of patients were treatment experienced before starting ART, and were not included in this analysis.

The percentage of men starting ART has remained around 30% over the 5 years of enrolment in the province, with a very slight increase over time. The gender breakdown of children is not routinely recorded but reviews of paediatric sentinel site data reveal that the gender breakdown of children starting ART is roughly even. Overall, 22.7% of adults began ART with a CD4 count below 50 cells/µl while 45% of children started ART with a CD4 count below 15% of total lymphocytes.

After 4 years on ART, 76% of adults remained in care (Fig. 4 and Table 1). For each duration on ART, this absolute estimate was based only on the data for those patients who started that number of months previously. Using the weighted survival data, the Kaplan–Meier estimate of retention in care was 72.0% at 4 years on ART with a narrower confidence interval (95% confidence interval, CI: 68.0–75.6). A similar analysis of paediatric outcomes (Fig. 5 and Table 2) revealed 81.5% (95% CI: 75.7–86.1) of

Fig. 4. **Estimates of retention in care for treatment-naive adults**



ART, antiretroviral therapy.

Table 2. **Estimates of retention in care for treatment-naive children**

Duation on ART (months)	0	6	12	18	24	30	36
Total children starting ART	1 709	1 216	770	371	72	51	35
Started before		30 Jun 2005	31 Dec 2004	30 Jun 2004	31 Dec 2003	30 Jun 2003	31 Dec 2002
Deaths since start[a,b]		84 (7.4)	68 (9.8)	32 (9.3)	4 (5.7)	4 (8.2)	4 (11.8)
Lost to follow-up since start[b,c]		22 (1.9)	23 (3.3)	19 (5.5)	4 (5.7)	3 (6.1)	2 (5.9)
Transfers out since start[b,d]		84 (6.9)	77 (10.0)	27 (7.3)	2 (2.8)	2 (3.9)	1 (2.9)
Remaining in care – absolute[e,f]		90.6 (88.8–92.3)	86.9 (84.1–89.3)	85.2 (81.0–88.8)	88.6 (78.7–94.9)	85.7 (72.8–94.1)	82.4 (65.5–93.2)
Remaining in care – cumulative[g,h]		90.9 (89.3–92.4)	88.5 (86.5–90.2)	84.8 (81.9–87.2)	83.5 (79.4–86.8)	81.5 (75.7–86.1)	81.5 (75.7–86.1)

ART, antiretroviral therapy.
[a] Deaths since start = deaths / (total - transfers out).
[b] Values in parentheses are percentages.
[c] Lost to follow-up since start = losses to follow-up / (total - transfers out).
[d] Transfers out since start = transfers out / total.
[e] Remaining in care = (total - losses to follow-up - deaths - transfers out) / (total - transfers out).
[f] Values in parentheses are exact binomial confidence intervals.
[g] Weighted Kaplan–Meier estimate.
[h] Values in parentheses are Greenwood point-wise confidence intervals.

children remained in care after 3 years. If looking only at those children who had been in care for the entire 3 years, the estimate is comparable (82.4%). In both adults and children starting ART, mortality was highest in the first 6 months on therapy.

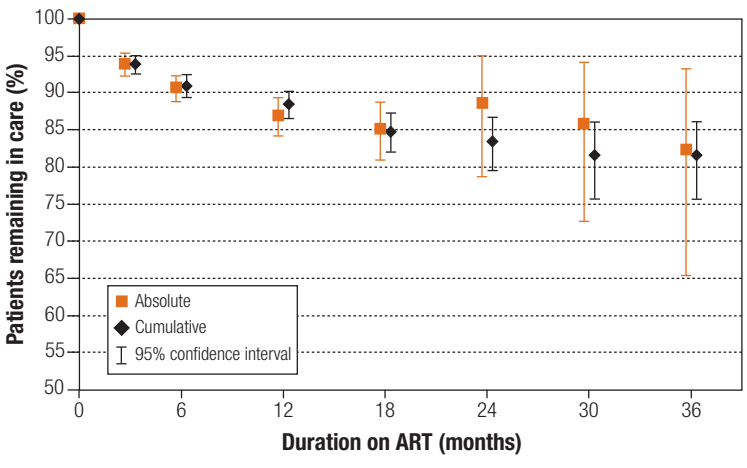
The first laboratory metric reported on is the proportion of tests that are done when they should be done. This is a proxy for quality of care. Results were received in the cohort system for four out of five patients who should have received these tests (Table 3). There is currently a slight drop-off in the test completion proportion as the duration on ART increases.

Looking at adult laboratory outcomes, of those tested, 90.6% of adults achieved virological suppression by 6 months on ART (Table 3). Although the proportion of patients on second-line regimens increases with duration on ART, and the data system does not distinguish which viral loads are done in patients on first-line versus those on second-line, for all patients combined this percentage remained at 85% or above until 4 years on ART. At 2 years on ART, 3.7% of adults were on second-line, rising to 17.9% at 4 years on ART. Combining all adult patients together, irrespective of the duration on ART, 1.3% of patients were reported to be on second-line regimens at the end of 2005. At the end of the first year on treatment, 74.7% of adult patients had attained a CD4 count above 200 cells/µl or greater, rising to 86.0% at 2 years on ART and 95.3% at 4 years on ART.

The proportion of children achieving virological suppression ranged between 70% and 80% during the 3 years' duration of follow-up (Table 3), while 7.4% had been changed to second-line by 3 years on ART. By 2 years on ART, 85.7% of children had achieved a CD4 greater than 20% of lymphocytes.

As the rate of enrolment increased in the province (Fig. 1 and Fig. 2), the severity of illness in patients starting ART decreased, evidenced by the lower proportion with CD4 cell counts below 50 cells/µl at ART initiation. In 2001 and 2002, half the adult patients starting ART had a CD4 count below 50 cells/µl, whereas this fell to 21.5% in 2005. This, coupled with the expansion of the programme into different

Fig. 5. **Estimates of retention in care for treatment-naive children**



ART, antiretroviral therapy.

Table 3. **Laboratory outcomes in treatment-naive adults and children on ART**

Duration on ART (months)	6	12	18	24	30	36	42	48
Adults in care and on ART	7 100	3 738	1 640	651	414	237	139	56
On second-line (%)	0.5	1.8	3.3	3.7	4.8	9.7	10.8	17.9
Viral loads done	5 979	3 330	1 401	573	343	171	93	44
Completion (%)	84.2	89.1	85.4	88.0	82.9	72.2	66.9	78.6
< 400 copies/ml (%)	90.6	89.0	88.1	88.3	88.0	86.0	84.9	90.9
95% CI	89.8–91.3	87.9–90.0	86.3–89.7	85.4–90.8	84.1–91.3	79.8–90.8	76.0–91.5	78.3–97.5
CD4 counts done	5 972	3 335	1 380	564	331	168	95	43
Completion (%)	84.1	89.2	84.1	86.6	80.0	70.9	68.3	76.8
≥ 200 cells/μl (%)	62.2	74.7	82.0	86.0	90.9	88.1	88.4	95.3
95% CI	60.9–63.4	73.2–76.2	79.9–84.0	82.9–88.8	87.3–93.8	82.2–92.6	80.2–94.1	84.2–99.4
Children in care and on ART	1 019	597	293	62	41	27	–	–
On second-line (%)	0.1	0.7	2.0	4.8	4.9	7.4	–	–
Viral loads done	822	531	245	53	28	20	–	–
Completion (%)	80.7	88.9	83.6	85.5	68.3	74.1	–	–
< 400 copies/ml (%)	72.7	72.3	74.7	77.4	78.6	75.0	–	–
95% CI	69.6–75.8	68.3–76.1	68.8–80.0	63.8–87.7	59.0–91.7	50.9–91.3	–	–
CD4 counts done	807	499	219	35	17	6	–	–
Completion (%)	79.2	83.6	74.7	56.5	41.5	22.2	–	–
> 20% lymphocytes (%)	57.5	71.5	74.9	85.7	88.2	83.3	–	–
95% CI	54.0–60.9	67.4–75.5	68.6–80.5	69.7–95.2	63.6–98.5	35.9–99.6	–	–

ART, antiretroviral therapy; CI, confidence interval.

communities, has seen mortality during the first 6 months on ART almost halved from 12.7% to 6.6% (Fig. 6 and Table 4). At the same time there has been an increase in the proportion of patients lost to follow-up. For patients starting ART in 2005, 4.7% had been lost to follow-up 6 months after starting ART.

Discussion

This analysis, based on routine data from a paper-based monitoring system, has demonstrated good cohort retention at 4 and 3 years in adults and children respectively, combined with favourable immunological and virological responses to therapy. As fewer patients have over time started ART with very low CD4 counts, so too has the mortality in the first 6 months of treatment declined.

The antiretroviral services in the Western Cape Province are representative of the national programme in South Africa, with the prior experience of innovator sites providing the opportunity to anticipate clinical outcomes and challenges that will be faced in the national programme.

The accumulated experience of these sites enabled the province to rapidly scale-up treatment in terms of both sites and patients around the time that the national programme became a reality. It is estimated that, in the final year under review in this paper, half of those newly in need of antiretroviral therapy were able to access it in the province. The falling proportion of adult patients with extremely low CD4 counts at enrolment reflects the impact of this scaling-up of ART provision.

The concurrent halving in early mortality at 6 months on ART, which accompanied the improved immunological status of adults starting ART, suggests that the high early mortality that is characteristic of programmes in the region is in part mediated by the extreme disease advancement at enrolment. This concurs with studies that have been able to stratify outcomes based on CD4 count categories.[2,5,12,13] Measures of the baseline CD4 count on enrolment may prove to be an extremely useful barometer of the extent to which programmes have caught up with the backlog in treatment in instances where the need for ART cannot be easily assessed.

A key limitation of this analysis, and all analyses of aggregate data, is the inability to stratify outcomes by individual baseline measures of disease severity. It is not possible from this analysis to determine if the decline over time in early mortality is fully mediated by measured improvements in the baseline clinical status of patients starting therapy.

Increasingly, patients lost to follow-up are outnumbering patients who are known to have died in developing country cohorts.[14] For this reason we believe that retention in care is the most useful metric for reporting on programme effectiveness. Retention in care in this analysis at 3 and 4 years on ART demonstrates unequivocally the huge survival benefit conferred by

the intervention. Most of the current simulation models that anticipate either patient numbers or the costs associated with ART have assumed a median of between 6 and 7 years survival on ART.[15] The current data at 4 years, where 7 out of 10 adult patients are still in care, suggest that these estimates are not overoptimistic, especially since many of the patients lost to care may well subsequently return to care, given the very tight definition of loss to follow-up.

Using 90 days without a clinical visit as the definition of loss to follow-up enables programmes to rapidly identify changes in this parameter and respond appropriately. It also fits in very well with the quarterly cohort reporting ensuring that, when reporting one quarter in arrears, all outcomes can be fully ascertained. On the other hand, many analyses have used longer durations (up to 1 year) without contact with the services to define loss to follow-up.[13]

Notwithstanding the definition used, a higher proportion of patients were lost to follow-up in the first 6 months on ART in 2005 compared to previously. It is probable that clinic patient loads exceeding manageable numbers in some clinics are affecting this. It is clear that retaining patients in constant care will become increasingly difficult as the service continues to expand, highlighting the importance of adherence promotion extending beyond the health services to the national and local media, political, social and religious platforms, as well as through community interventions. Decentralization of care to more facilities, and the appropriate resourcing of services, are key to ensuring that services at individual facilities remain of a manageable size and are able to appropriately retain patients in care.

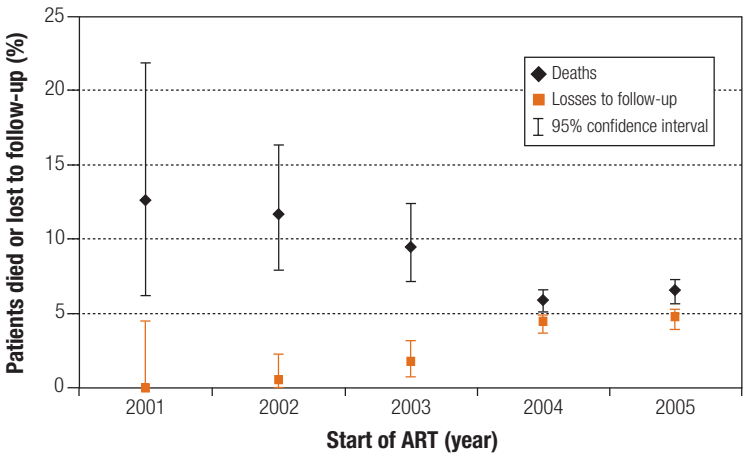
Even though most services retained some capacity to actively follow up patients lost to care during the period under review, it is probable that there remains residual under-ascertainment of mortality in the latter years as loss to follow-up increased.[16] It is further unknown to what extent in future the increased loss to follow-up will result in intermittent care and consequently increased virological resistance due to repeated treatment interruptions (which are known to be strongly associated with resistance).[17]

The slower increase over time in the numbers of children on ART compared to adults is entirely anticipated and does not imply that children are being underprovided for. Whereas the number of adults newly needing ART increases year on year, the number of children is decreasing due to successful implementation of a prevention of mother-to-child transmission programme.[18,19]

The virological outcomes are encouraging and suggest that at a population level the rates of viral rebound have not been alarming and are not undermining overall programme success. Nevertheless, with up to one in five patients requiring second-line therapy by 5 years on ART, it is clear that the higher cost of second-line drugs will impact on total programme costs as programmes mature.[20]

There have been many lessons learned in implementing the WHO monitoring approach. This system, based on registers and regular cohort analyses, shares many attributes with systems that have been in use for many years for monitoring tuberculosis programmes. Worth noting is the value of differentiating sentinel from routine

Fig. 6. **Temporal trends in baseline CD4 count survival and loss to follow-up at 6 months in adults starting ART**



ART, antiretroviral therapy.

Table 4. **Temporal trends in baseline CD4 count survival and loss to follow-up at 6 months in adults starting ART**

Number of adults[a]	80	248	524	3981	3508
Year started on ART	2001	2002	2003	2004	2005
CD4 < 50 cells/μl[b,c]	51.3 (39.8–62.6)	50.4 (44.0–56.8)	36.8 (32.7–41.1)	24.4 (23.1–25.8)	21.5 (18.8–20.6)
Mortality[c,d]	12.7 (6.2–21.8)	11.7 (8.0–16.4)	9.6 (7.2–12.4)	6.0 (5.1–6.6)	6.6 (5.6–7.3)
Loss to follow-up[c,e]	0.0 (0.0–4.5)	0.4 (0.0–2.2)	1.7 (0.8–3.2)	4.4 (3.7–4.9)	4.7 (3.9–5.3)

ART, antiretroviral therapy; CI, confidence interval.
[a] Number starting in year and reaching 6 months of follow-up.
[b] Proportion in starting cohort with CD4 counts < 50 cells/μl.
[c] Values in parentheses are exact binomial confidence intervals.
[d] Mortality = deaths by 6 months / (total in cohort - transfers out by 6-months).
[e] Loss to follow-up = losses to follow-up by 6 months / (total in cohort - transfers out by 6 months).

sites,[21] liberating the majority of sites from onerous data-collection procedures that are designed for clinical research rather than for supporting routine care. It has been our experience that, with viral loads being available, managers have paid little attention to CD4 count outcomes in assessing programme performance. We have also found that presenting the completion proportions for laboratory outcomes is an invaluable metric over and above the outcomes themselves in the subset of patients for whom results are available. Finally, one of the major challenges emerging as models of care evolve is the large number of patients moving between facilities, who, once transferred out, are censored in the cohort analyses.

The ability to report on cohort outcomes without electronic systems underscores the value of implementing a basics-first approach to routine monitoring. This does not mean that there is no role for the progressive and measured development of electronic systems[22] but rather that the basic building blocks that are required for a paper-based system are the same measures that will make electronic systems a success.[23]

Perhaps the most important lesson from the first 5 years of this programme is that implementing an ART programme in primary-care facilities from the outset is feasible and can achieve excellent clinical results. It is probable that the location of care in community clinics is one of the key factors contributing to the retention of patients in care.[24]

Looking to the future, if the Western Cape Province is to come close to the stated target of treating 80% of patients newly in need of therapy each year over the coming years, the annual number of patients enrolling in care will need to double while the total number of patients in care quadruples over a 5-year period. This will require even further task-shifting and expansion of the service platform, given that enrolment is already threatened by capacity constraints in the existing service platform.[25]

In conclusion, this paper has demonstrated excellent clinical outcomes 5 years after the Western Cape Province began offering ART in the public sector, validating the decision to make this a primary-care intervention from the outset. The WHO monitoring system has enabled the province to keep track of the intervention and of the performance of individual sites, while allowing space for more complex and durable solutions to be developed for the larger sites. ■

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Competing interests: None declared.

Résumé

Traitement antirétroviral et mortalité précoce en Afrique du Sud

Objectif Décrire les résultats à l'échelle provinciale et les tendances dans le temps du programme de traitement antirétroviral (ART) de la province du Cap-Occidental, 5 ans après son lancement et démontrer l'utilité du système de surveillance de l'OMS pour ce traitement.

Méthodes Le programme de traitement a débuté en 2001 au niveau de sites « novateurs ». Un rapide passage à l'échelle supérieure de la délivrance du traitement a commencé début 2004, à partir essentiellement d'établissement de soins de santé primaire. Des données relatives aux patients entamant un traitement ART ont été recueillies de manière prospective dans les registres des établissements de soins, ce qui a permis de constituer des rapports mensuels d'activité et des rapports trimestriels de cohorte. Les taux de rétention sous traitement et de mortalité, ainsi que les nombres de perdus pour le suivi et les résultats de laboratoire ont été calculés tous les 6 mois sous ART.

Résultats Fin mars 2006, 16 234 patients étaient sous traitement. L'analyse de cohorte a porté sur 12 587 adultes et 1709 enfants. Les femmes représentaient 70 % des adultes inclus dans l'étude. Après 4 et 3 ans sous traitement ART, respectivement 72,0 % des adultes (intervalle de confiance à 95 % : 68,0-75,6) et 81,5 % des enfants (IC à 95 % : 75,7-86,1) étaient encore sous traitement. Le pourcentage des adultes débutant le traitement ART avec une numération des CD4 inférieure à 50 cellules/µl est tombé de 51,3 % en 2001 à 21,5 % en 2005, tandis que la mortalité à 6 mois passait de 12,7 % à 6,6 %, baisse en partie compensée par l'augmentation du nombre de perdus pour le suivi (atteignant 4,7 % à 6 mois en 2005). Plus de 85 % des adultes dépistés présentaient une charge virale inférieure à 400 copies/ml tous les 6 mois jusqu'à 4 ans sous ART.

Conclusion La dispensation par ce programme des soins dans des sites de soins de santé primaire était associée à un taux de rétention satisfaisant, tandis que l'élargissement du programme était associé à une réduction de la mortalité précoce.

Resumen

Tratamiento antirretroviral y mortalidad temprana en Sudáfrica

Objetivo Describir los resultados y las tendencias temporales a escala provincial del programa de tratamiento antirretroviral (TAR) de la Provincia de El Cabo Occidental a los 5 años de su puesta en marcha y demostrar la utilidad del sistema de vigilancia de la OMS para el TAR.

Métodos El programa de tratamiento dio comienzo en 2001 a partir de establecimientos innovadores. La rápida expansión del suministro de TAR comenzó a principios de 2004 y se centró predominantemente en los servicios de atención primaria. Los datos sobre los pacientes que comenzaron el TAR se reunieron de forma

prospectiva en los registros de los centros, a partir de los cuales se elaboraron informes mensuales transversales de actividad e informes trimestrales de cohortes. La retención en el sistema de atención, la mortalidad, las pérdidas para el seguimiento y las variables de laboratorio se calcularon considerando los periodos de 6 meses de TAR.

Resultados Al final de marzo de 2006 se estaba tratando a 16 234 pacientes. El análisis de cohortes abarcó a 12 587 adultos y 1709 niños. Las mujeres representaban el 70% de todos los adultos estudiados. Al cabo de 4 y 3 años de TAR, respectivamente, el 72,0% de los adultos (intervalo de confianza del 95%, IC95%: 68,0–75,6) y el 81,5% (IC95%: 75,7–86,1) de los niños seguían atendidos. El porcentaje de adultos que comenzaron el TAR con recuentos de CD4 inferiores a 50 células/µl cayó del 51,3% en 2001 al 21,5% en 2005, mientras que la mortalidad a 6 meses cayó del 12,7% al 6,6%, compensada en parte por un aumento de las pérdidas para el seguimiento (que alcanzó el 4,7% a los 6 meses en 2005). Más del 85% de los adultos analizados presentaron cargas virales inferiores a 400 copias/ml a intervalos de 6 meses durante los 4 años de TAR.

Conclusión La ubicación de la asistencia en los centros de atención primaria en este programa se asoció a una buena retención de los pacientes, mientras que la expansión del TAR se asoció a una disminución de la mortalidad temprana.

ملخص

المعالجة بمضادات الفيروسات القهقرية والوفيات المبكرة في جنوب أفريقيا

الهدف: توضيح النتائج على مستوى المقاطعة، والاتجاهات الزمنية لبرنامج المعالجة بالأدوية المضادة للفيروسات القهقرية في مقاطعة الرأس الغربي بعد مضي خمس سنوات من إدخال البرنامج، وإبراز جدوى نظام المنظمة الخاص برصد المعالجة بمضادات الفيروسات القهقرية.

الطريقة: بدأ برنامج المعالجة في عام 2001 من خلال مواقع مستحدثة. كما بدأ تسريع وتيرة الارتقاء بتقديم المعالجة بمضادات الفيروسات القهقرية في مطلع عام 2004، في مرافق الرعاية الأولية بشكل أساسي. وتم تسجيل المؤشرات الخاصة بالمرضى الذين بدءوا في تلقي المعالجة بمضادات الفيروسات القهقرية في سجلات المرافق، مما ساعد على تجميع التقارير الأترابية ربع السنوية، والنشاط الشهري. وتم احتساب معدلات استبقاء المرضى تحت الرعاية، والوفيات، والفقدان أو التسرب من المتابعة، والنتائج المختبرية كل ستة أشهر من المعالجة بمضادات الفيروسات القهقرية.

الموجودات: بنهاية آذار/مارس 2006، وجد أن عدد المرضى تحت الرعاية يبلغ 16 234 مريضاً. فقد تضمن التحليل الأترابي 12 587 بالغاً، و1709 من الأطفال، بينما مثلت النساء 70% من البالغين المدرجين بالتحليل. وبعد مضي أربع سنوات كانت نسبة الاستمرار في تلقي الرعاية بين من يتلقون المعالجة بمضادات الفيروسات القهقرية من البالغين 72.0% (بفاصل ثقة 95%، إذ تراوح معدل الأرجحية بين 68.0 و75.6)، وبعد 3 سنوات كانت نسبة الاستمرار تحت الرعاية بالنسبة للأطفال الذين يتلقون المعالجة بمضادات الفيروسات القهقرية 81.5% (بفاصل ثقة 95%، إذ تراوح معدل الأرجحية بين 75.7 و86.1). فنسبة البالغين الذين بدأوا المعالجة بمضادات الفيروسات القهقرية وكان عدد CD4 لديهم أقل من 50 خلية لكل مكرولتر، انخفضت من 51.3% في عام 2001 إلى 21.5% في عام 2005، في حين انخفضت الوفيات خلال 6 شهور من 12.7% إلى 6.6%. ولكن هذه النتيجة تكافأت جزئياً مع زيادة عدد من فقدوا وتسربوا من المتابعة (لتصل إلى 4.7% في خلال 6 شهور من عام 2005). فأكثر من 85% من البالغين الذين تم اختبارهم كان عبء الفيروس لديهم أقل من 400 نسخة لكل ملي لتر على مدى 6 شهور من المعالجة بمضادات الفيروسات وحتى مرور أربع سنوات من استمرار المعالجة بمضادات الفيروسات القهقرية.

الاستنتاج: إن وضع الرعاية في مواقع الرعاية الأولية في هذا البرنامج يصاحبه معدلات جيدة لاستبقاء المرضى في الرعاية، وفي الوقت نفسه فإن الارتقاء بتقديم المعالجة الدوائية بمضادات الفيروسات القهقرية يصاحبه تقلص الوفيات المبكرة.

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Chapter 3: Discussion / synopsis

This thesis has resulted in a series of five linked papers which all contribute to addressing the original aims of the thesis. The synopsis below reflects on how the papers have contributed to addressing these, in the light of the rapid accumulation of data and analyses on ART outcomes in the region. In order not to repeat the discussion points raised in each article, the synopsis attempts to draw out themes from the integrated body of work, and updates discussion points where additional data have become available subsequent to the publication of the papers included in the thesis. The synopsis also introduces data from other studies where there are gaps in the included papers.

The effectiveness of ART in Khayelitsha and the Western Cape Province at averting mortality

The over-riding concern emerging related to evaluating ART outcomes in Southern Africa is that the poor ascertainment of mortality in scale-up settings may be masking poor effectiveness. The findings from this thesis that utilise linkages to the death registry demonstrate that after substantial scaling up of care, four out of five patients are alive at five years, in spite of increasing loss to follow-up.[250] Compared to the anticipated natural history without ART, the benefits are profound.[251-253] Data from the Entebbe cohort in Uganda from the pre-ART era, estimate that 8% of patients with an initial median CD4 count of 75 cells/μL were still alive after five years.[253]

The impact on mortality estimates of correcting for deaths in those lost to follow-up

This thesis found high cumulative proportions of patients lost to follow-up in Khayelitsha (23.4% at five years). One third of those lost to follow-up had died when traced through death registry linkage. The increase in the cumulative mortality estimate at five years is however relatively modest with and without the adjustment for deaths in those lost to follow-up (20.9% vs. 15.5%). There are two explanations for this, not fully considered in the discussion of the paper. Firstly, the rapidly

increasing enrolment year-on-year, evidenced both in Khayelithsa and the Western Cape, result in the cohorts being skewed towards patients followed for shorter durations on ART, with consequently lower overall proportions lost to follow-up than the distal cumulative estimates. The second explanation is that the probability of having died in patients lost to follow-up is related to the duration of follow-up when lost, with patients in care for longer when lost less likely to have died. Prior to the availability of death-registry linked data, studies tracing patients lost to care have not been able to systematically describe this changing probability by duration of ART or calendar period.[97 131-134] Attempts to use once-off tracing studies to adjust mortality estimates are likely to be highly dependent on the characteristics and calendar period of the utilised tracing study.

The corrected mortality in Khayelitsha compared to other data from Africa and globally

As reviewed earlier, there are two African studies that have formally reported five year outcomes. For patients starting ART more than five years ago in Botswana, 21% had died and 22% had been lost to follow-up by five years, compared to the 21% corrected mortality estimate in Khayelitsha. As demonstrated in Khayelitsha and the Western Cape however, subsequent cohorts of adults starting ART in Botswana may have had improved survival compared to the first years of ART provision. The Khayelitsha corrected survival at five years is also slightly higher than the estimate from the Senegalese government programme, prior to considering loss to follow-up in this cohort,[104] but is still almost double the appropriate comparative estimates from a prognostic model from a collaboration of wealthier country cohorts (the ART Cohort Collaboration) presented in the literature review.

Determinants of mortality in Khayelitsha and the Western Cape

Comparative early mortality between settings and time periods

The analyses included in this thesis have not directly included comparisons to outcomes from other settings, although data from the Western Cape have been a major contributor to, or the basis of such comparisons.[118 127] Probing the differences

in mortality between wealthy country and African cohorts, after adjustment for disease severity, provides a useful frame however for considering context-specific determinants of mortality. The discussion below reflects on these differences based on both the data presented in this thesis and related studies.

Some of the putative reasons for the differences in early mortality between settings were reviewed in the literature review. In the discussion of the published declines in early mortality over time in the Western Cape,[77] it was reflected that the aggregate data did not enable an analysis of whether or not the declines could be fully ascribed to changing disease severity at ART initiation.

The measures of disease advancement available for adjustment of comparative analyses (whether compared between settings or between time periods in the same settings) may not be adequate to fully adjust for differences in patients characteristics. The first possibility is one of residual confounding – that there may be unmeasured characteristics that describe disease severity that are not fully captured by clinical stage and CD4 count. For example, the number of stage defining illnesses in patients with a given WHO clinical stage may be greater in one context or time period compared to another. The mix of individual stage-defining illnesses may differ between settings in patients with the same clinical stage. There is also a possibility of misclassification bias, whereby the availability of specialist clinical care may result in a higher probability of stage-defining illnesses being diagnosed in some contexts compared to others. Finally, there is a possibility of selection bias, whereby patients with very low CD4 counts may represent average patients in one setting, and unusually robust patients in another, as evidenced by the comparative distribution of CD4 counts when initiating ART in Khayelitsha and Switzerland (Figure 3).[254]

If these explanations held true, one might have expected the temporal trends in early survival in Khayelitsha, after adjustment for disease severity and correction for deaths in those lost to follow-up, to have demonstrated an improvement with calendar period. We found, however, that whereas in crude terms survival improved with calendar period, there was no improvement with calendar period in early or late mortality after adjustment for CD4 count and AIDS at ART initiation.[250] This

finding is difficult to interpret, as there have been dramatic changes in the scale of the service with calendar period, which could also have resulted in worsening care, or poorer ascertainment of markers of clinical severity.

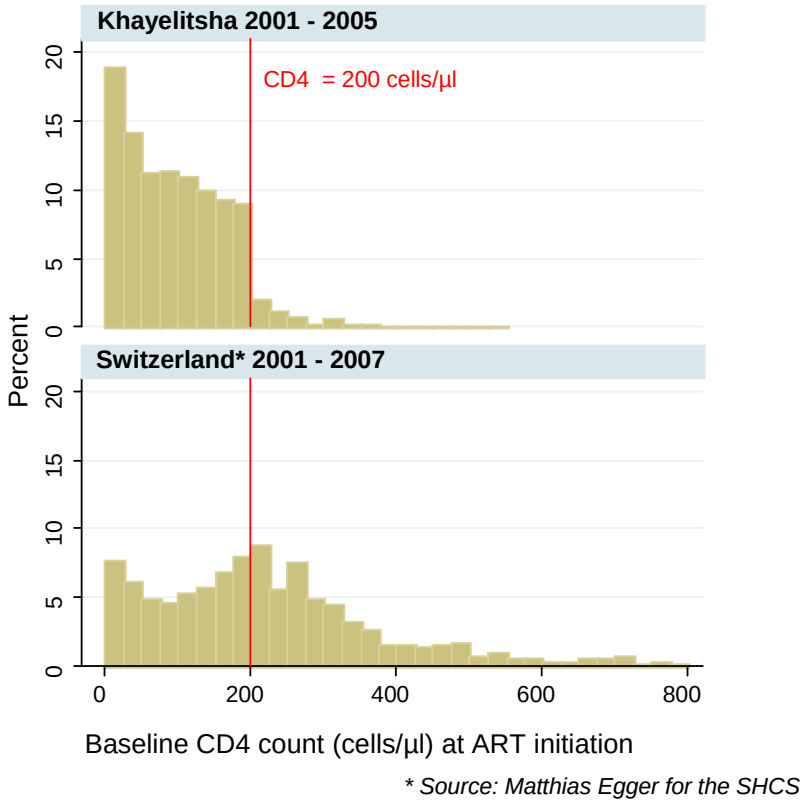

Figure 3. Comparative baseline CD4 counts at ART initiation: Khayelitsha and Swiss HIV Cohort Study

The other difference between settings that is often implicated in discussions on this differential early mortality, is the much higher prevalence at baseline and incidence during follow-up of tuberculosis in Southern Africa. This thesis has presented data demonstrating that patients initiating ART with prevalent tuberculosis are not at a higher risk of mortality compared to those without prevalent tuberculosis after adjustment for disease severity.[166] Although another study from Cape Town presented evidence of a higher mortality in those with tuberculosis, this was a crude comparison not accounting for the lower CD4 counts and more advanced clinical stage in those with tuberculosis.[239] Tuberculosis is however often identified as the cause of death in patients on ART.[241]

In 10 out of 13 patients in whom tuberculosis was identified as the cause of death in a Ugandan study, treatment for tuberculosis was not commenced prior to ART initiation, five of whom were asymptomatic at the start of ART.[238] There is increasing evidence as to the prevalence of undiagnosed tuberculosis at the start of ART in patients without symptoms suggestive of tuberculosis – in Khayelitsha 7% of patients starting ART who were asymptomatic after a systematic screen for symptoms of tuberculosis were found to have *Mycobacterium tuberculosis* confirmed on sputum culture.[255] It is highly likely that new or unmasked tuberculosis in patients recently started on ART contribute substantially to mortality in the Western Cape and similar contexts.

Finally it is possible that the availability and quality of clinical care differs between settings, resulting in mortality differences that are accentuated as patients are sicker and are more likely to require acute care and hospitalisation. There is evidence that aside from HIV, the background mortality for adults of the same ages as those starting ART in South Africa is twice that in Switzerland.[127]

Other domains of effectiveness in Khayelitsha and the Western Cape

Virological response

The viral load responses described in the Khayelitsha outcomes paper [250] are broadly similar to those in the larger Western Cape province-wide programme.[77] Although biased by the exclusion of patients in whom viral loads were not measured, the consistent recording of more than 80% of patients with viral loads below 400 copies/mL through the first few years of ART is re-assuring in terms of adherence being maintained in spite of the scaling up of care and increased patient volumes. Further reassurance, while not forming part of this thesis, comes from a comparison of time to virological suppression and rebound between two Western Cape cohorts and the Swiss HIV Cohort Study.[127] In this comparison, which included data from Khayelitsha, there was no difference in either measure between settings. Confirmed virological failure is discussed further below as part of regimen durability.

Immunological response

The presentation of CD4 count response conditioned on viral load suppression was identified as a unique opportunity in South African cohorts, due to the availability of paired viral load and CD4 count measures, and was demonstrated in Khayelitsha to be consistent with the responses described in Europe and North America.[250] A collaborative analysis in the ART-LINC collaboration in which viral load data were not available, showed a plateau in CD4 count recovery at 3 years in all strata of baseline CD4 count except for those patients initiating ART at a CD4 count of >=300 cells/μL.[123] Some of this inference may be an artefact of the fractional polynomial functions fitted to the response in each stratum, in addition to the inability to exclude responses in patients who might have been failing virologically. Nevertheless, it would be valuable to further explore the CD4 count response conditioned on virological suppression in Khayelitsha in subgroups of patients, particularly those with extremely low CD4 counts (<25 cells/μL) on ART initiation.

The observation in both the Khayelitsha and ART-LINC studies that CD4 count response was greater in women than in men has also been described in other settings.[256]

Effect of ART on tuberculosis and other HIV-associated events

This thesis did not seek to explore the effect of ART on morbidity or HIV-associated events, due in part to the poor availability (except in the case of tuberculosis) of data on individual clinical diagnoses during follow-up. In addition to the studies from the same context on the reduction in tuberculosis on ART described earlier,[75 119 232-233] there has been a conference report on the reduction in tuberculosis on ART in Khayelitsha (Boulle, 2004),[257] demonstrating that the incidence rate ratio of tuberculosis on ART compared to pre-ART was either 0.32 or 0.46 depending on the inclusion or exclusion of the first month after referral or after ART initiation. This question is the subject of ongoing analyses on the Khayelitsha data, in which marginal structural models are being used to adjust for time-varying confounding by CD4 count which predicts tuberculosis and is itself affected by prior ART. Only one study in adults and one in children have to date reported on the causal effect of ART on tuberculosis with appropriate adjustment for time-varying confounding.[75 258] Both

studies reported smaller relative reductions in tuberculosis risk on ART than preceding studies.

Although no analyses are presented on the effect of ART on other HIV-associated conditions in Khayelitsha, the Khayelitsha cohort was one of the early cohorts to confirm the effect of ART on quality of life.[259]

Effect of ART on risk behaviour of those on ART and beyond those receiving ART

One of the papers in this thesis was originally intended to explore the broader community impact of ART availability.[260] Even though ART had been available earlier and more widely in Khayelitsha than in most other Southern African townships at the time of the survey, more than half the respondents had not heard of ART, and of those who had, only 14% of men and 22% of women knew someone on ART at the time. Although many more people are likely to have heard of ART and to know someone on ART currently given the many fold increase in treatment since then in Khayelitsha, attempts to link ART availability to more openness about HIV and behavioural change are fraught with difficulty in cross-sectional studies. As argued in the paper, there is now sufficient agreement on the imperative for treatment for the purposes of averting mortality and morbidity, not to have to demonstrate an impact on prevention through behaviour modification either for those on ART or those not on ART. Looking at behaviour modification for patients on ART, there are few rigorous studies, and as yet evidence points towards positive rather than negative impacts on risk behaviour.[261] Research in Cape Town has demonstrated high levels of risk behaviour amongst adults initiating ART,[262] but also substantial declines in risk behaviour over the first year of ART.[263]

Regimen durability and tolerability

A number of the papers included in this thesis directly assess the tolerability and durability of the regimens used in the Khayelitsha and Western Cape ART programmes.[126 166 250] While demonstrating the effectiveness of ART in terms of survival has been an important contribution validating the investment in providing

this intervention on such a large scale, the analyses addressing ART regimens have had a more direct impact on programme design.

Tolerability of stavudine

Early reports identified a high number of diagnoses of lactic acidosis in patients in South Africa initiating ART on stavudine-containing regimens.[147] The cohort analysis from Khayelitsha and Gugulethu was one of the first to be able to quantify the risk of symptomatic hyperlactataemia or lactic acidosis (SHLA), and assess baseline associations with the development of this condition.[126] In particular, the anecdotal concerns about overweight women being predisposed to this complication were documented and the excess risk quantified. A study from a hospital-based cohort in Johannesburg reported soon after the Western Cape study,[145] with the incidence of SHLA reported as 31 per 1000 patient years compared to 19 in the Western Cape study. The higher incidence in Johannesburg might have been the result of a younger cohort, with more person time at risk between 6 and 18 months on ART, the duration on ART when the majority of cases are diagnosed.[152] A case control study in the Western Cape, which incorporated some of the incident cases from the cohort study, confirmed the association with higher weight and body mass index (BMI) in women (adjusted odds ratio of 19 comparing women initiating ART with a weight above 75kg compared to those below 60kg, compared to the adjusted hazard ratio of 36 for the same comparison in the cohort study).[264] The hospital cohort in Johannesburg did not report on associations with SHLA, but reported that 35% and 20% of patients with lactic acidosis and symptomatic hyperlactataemia respectively had BMIs above 30.

The Western Cape Province instituted a range of guideline changes to address the risk factors for SHLA, resulting in a dramatic decline in referred cases of SHLA, and related deaths.[265] These changes included the scrapping of the d4T dose escalation in patients above 60kg, the preferential use of AZT in women with high BMIs, clinical training and the use of point-of-care lactate metres in primary care settings. As discussed in the literature review, the WHO amended their guidelines similarly to avoid the higher dose of d4T.[266] A South African study subsequently found no

difference in virological suppression in patients above 60kg before and after the guideline amendment.[267]

Aside from SHLA, compared to other first line antiretrovirals, the notable feature of treatment-limiting toxicities to stavudine is that they were demonstrated to continue to accumulate with time on ART, especially peripheral neuropathy and lipodystrophy. In the context of needing to minimise the requirements for clinical care in order to facilitate the scaling up of ART, the disadvantages of d4T with respect to toxicity may counterbalance the advantages in terms of cost, accessibility and co-formulation.

Effectiveness of nevirapine with and without concurrent tuberculosis treatment

Both the analysis of nevirapine effectiveness in patients starting ART while co-infected with tuberculosis,[166] as well as the overall analysis of associations with virological failure in the Khayelitsha cohort,[250] identified that NVP use as choice of NNRTI was associated with inferior virological outcomes. As discussed in both papers and the literature review, these findings are not unique in observational settings,[79 161 167] and do not conflict with clinical trial data.[160]

The association described in this thesis between being on treatment for tuberculosis at the start of ART and inferior effectiveness of nevirapine-based ART is less supported by other studies. Some studies reporting a lack of this association have however been underpowered to detect such an association.[268-269] Results of ongoing clinical trials are awaited. A trial in Thailand found equivalent proportions of tuberculosis co-infected patients remaining suppressed on NVP and EFV after 48 weeks.[270] Although a higher proportion of patients on NVP had NNRTI plasma concentrations (C_{12}) below the recommended therapeutic minimum than those on EFV, there was no evidence of a difference in virological outcomes (n=71 per group). It is unclear how generalisable Thai studies on drug interactions are to Southern Africa. A trial of different once daily regimens in co-infected patients confirmed the findings of the Khayelitsha study, but differed from local practice in that NVP was dosed daily as opposed to twice daily.[271] The strongest effect seen in the Khayelitsha study was on confirmed virological failure (two consecutive viral loads above 5000 copies/mL), whereas most other studies have looked at virological

response in the first year. It is possible that confirmed failure is more likely to be indicative of NNRTI resistance, and that associations with this are less prone to dilution by adherence and other issues. One putative mechanism offered in discussion of the Khayelitsha findings was that the lead-in dose of NVP in patients who already have hepatic induction by rifampicin could be resulting in sub-therapeutic NVP levels in the first two weeks of therapy. A Thai study sought to compare standard NVP dosing to an increased dose of NVP both during the lead-in period (200mg bd) and subsequently (300mg bd). The higher dosed group had more favourable NVP levels, but also more hypersensitivity reactions.[272]

In spite of these documented concerns regarding comparative NVP effectiveness, NVP-based ART was nevertheless highly effective in the presented analyses. The use of alternatives is also limited due to the costs of both EFV and boosted protease inhibitors, as well as the concerns regarding EFV use in women at risk of conception.

Durability of current first-line regimens

As reviewed in the literature review, the South African and Botswana national treatment programmes are unique in the region in providing for regular viral load monitoring. One of the contributions of this thesis has been to explore how these guidelines are being applied, as well as the time to meeting guideline definitions of virological failure, and the time to switching therapy in patients who meet this definition. Both the Khayelitsha cohort and the Western Cape provincial programme have been able to report these outcomes at longer durations on ART than most similar programmes. The proportion of patients failing therapy and starting second-line therapy at five years is lower than many anticipated when cohorts such as Khayelitsha first started offering ART. Combined however with the massive scaling up of ART, the modest proportions failing ART will still result in very large absolute numbers of patients requiring second-line therapy, with important consequences on programme costs.

The delay between meeting guideline definitions and starting patients on second-line ART could compromise the limited benefits, described in the literature review, that the viral load-based switching strategy has in terms of averting resistance to alternate

or recycled thymidine analogue NRTI's. These delays reflect the difficulties in tightly applying guidelines that are based on laboratory measures in the context of busy clinical settings where patient numbers are constantly expanding. The laboratory, clerical and financial challenges to ensuring the completeness and ready availability of twice-yearly viral load tests have lead some scientists to suggest less frequent viral load monitoring in South Africa.[273]

Implications for regimen choices and laboratory monitoring

The studies in this thesis have raised concerns about the safety of d4T, the effectiveness of NVP, and have demonstrated the difficulties in tightly following the guidelines for switching patients on virological grounds. Although this thesis did not seek to review health system issues related to the scaling up of ART, all of these findings support moving towards simplified guidelines that recommend the use of both d4T and NVP in fewer circumstances, and less frequent laboratory monitoring of ART. A once daily regimen of TDF, 3TC and EFV is now the most commonly prescribed regimen in wealthier countries. If utilised more widely in Southern Africa, this regimen would minimise the risks associated with d4T and NVP, would spare more future treatment options, would ease supply chain management, and would assist in patient adherence due to the lower pill burden. The less frequent laboratory monitoring would save costs, as well as the burden on both clerical staff and patients in being monitored twice annually. The averted viral load tests could allow the introduction of an early viral load test to assist in assessing adherence and allocating patients to less intensive follow-up if virologically suppressed. The findings from the studies included in this thesis constitute a small but important contribution to informing these discussions.

Scalability of ART and generalisability of findings

The paper included in this thesis on the Western Cape provincial outcomes, two years after the launch of the national programme, demonstrated how the early results from cohorts such as Khayelitsha were sustained when scaled up throughout the province.[77] The Khayelitsha sub-district has undergone large year-on-year increases in patient enrolment itself, and it is reassuring that in the cohort, survival has not

deteriorated with calendar time after adjustment for other factors associated with survival.[250] Not documented in detail in the thesis, Khayelitsha has, of all services in the province, undergone the most dramatic changes in the model of ART care provision. Some years ago we reflected on the challenges to scaling up enrolment further in Khayelitsha without expanding the service platform.[274] The service platform has indeed expanded to the smaller clinics run by the City of Cape Town, but enrolment in the existing provincially run community health centres has also increased dramatically in spite of unchanging physical and human resources. The service changes alongside which outcomes have not deteriorated have included the fast-tracking of stable patients through afternoon clubs, more efficient medicine dispensing, wider spacing of appointments, and less intensive counselling and community follow-up.

In most instances achieving increases in ART services as seen in the Western Cape has either compromised information systems to the extent that robust outcome reporting is no longer possible,[275] or has required huge investments in information technology and associated human resources in order to be able to reflect the success of scaling-up therapy.[101] The Western Cape study has demonstrated how de-linking research and sentinel surveillance from routine monitoring enables a more rational and simplified routine monitoring system to be implemented. Although the paper-based monitoring system in use is currently under immense pressure due to patient numbers and duration of follow-up in many facilities, complete cohort data are today still available on all 60,000 patients on ART in the province. The trends described until mid-2006 (published in 2008) and included in this thesis have continued and in some cases (such as rising loss to follow-up and declining mortality) been accentuated. Overall the programme has continued to scale better than initial expectations.

Comparing the papers on Khayelitsha and the province, many of the outcomes from the province are similar to or better than those in Khayelitsha, demonstrating that outcomes have not been compromised with the wider availability of ART in the province. For example virological suppression to below 400 copies/mL in adults at 12, 24 & 36 months was 88, 87 & 88% in Khayelitsha and 89, 88 & 88% in the

province as a whole. This also helps establish the generalisability of the findings from Khayelitsha for other settings.

The survey that was conducted in Khayelitsha and included in this thesis, clearly confirms that the referral area for the Khayelitsha cohort is representative of urban townships: only a third of respondents were in formal housing, and at least a quarter of men and almost half of women were unemployed. High school completion was low notwithstanding that the survey included some respondents who were still at school. Risk factors for HIV acquisition such as multiple concurrent partnerships were in keeping with surveys in other South African townships.

Although per capita expenditure on health is highest in the Western Cape compared to other Provinces in South Africa, Khayelitsha is one of the most underserved sub-districts in the Western Cape, and it is probable that it is much more reflective of challenges in other urban settings in South Africa and possibly the region than is the case for the province as a whole.

Limitations and gaps in the thesis

Health system issues

This thesis has sought to address the effectiveness and scalability of ART in the Western Cape Province, but has not covered health system aspects of ART provision in any detail. Although the focus has been on clinical outcomes and clinical programme design, questions of feasibility and sustainability require a more detailed consideration of the health system capacity, financing, human resource requirements, and the evolution of the model of care for ART provision in the setting.

There are however a number of publications based on the Khayelitsha project which are not formally part of this thesis, but which do address these issues in part. In 2006, a cost-effectiveness analysis was published which drew on effectiveness, quality of life and cost data drawn directly from the Khayelitsha project.[276] At the time it was the only such study in which all these domains were based on primary data collected from the same patients. A subsequent analysis considered the delivery of ART within

a budget constraint.[277] Also in 2006, the Khayelitsha project reflected on the future challenges facing ART provision.[274] The move to less intensive adherence counselling was described, and the need for further task shifting and expansion of the service platform in order to meet future enrolment targets was highlighted. The first paper in this thesis demonstrates that for the most part, these shifts did indeed occur, and makes reference to the less intensive patient preparation, whilst retaining an overall frame of a patient-centred approach to adherence promotion.[250] A report on four different ART services in the Western Cape, including Khayelitsha, sought to explore the relationship between the model of care for ART service provision and patient outcomes, concluding that the human factors other than the model itself were the most important factors related to efficient and effective service provision.[278] Finally, the comparison between Switzerland and the Western Cape, referred to a number of times above, looked more broadly at the public health approach compared to the standard of care in wealthier countries.[127]

Effect of ART on opportunistic infections and disease progression

This thesis has examined mortality and laboratory outcomes, but has not addressed disease progression in terms of new HIV-associated conditions or AIDS-defining illnesses. In part, deficiencies in the systematic recording of HIV-associated events hinder the ability to look at disease progression in this way. There are nevertheless some additional outcomes that are recorded accurately enough to explore, which have not been described in this thesis, most notably tuberculosis.

Besides the effect of ART on HIV-associated conditions, the other gap in the scope of this thesis is the effect of HIV-associated conditions at ART initiation on other ART outcomes. Although the presence of AIDS-defining illnesses has been included in multivariate models for associations with early and late mortality,[250] the number and nature of specific conditions has not been included in models of associations with mortality. In spite of the concern that the ascertainment and accurate recording of these conditions has deteriorated with time, there remains a need to explore this in further detail.

Conclusion and recommendations for future research

This thesis has presented five papers which broadly describe the population, the outcomes and the associations with outcomes in the Khayelitsha and Western Cape ART programmes.

The first contribution of this thesis has been to describe in detail the clinical effectiveness of ART, and how this changes over time. Both the Khayelitsha and Western Cape cohort analyses presented in this thesis provide benchmarks as to the real world effectiveness of ART in the region, and considerable reassurance that the anticipated benefits of ART have not to date been completely eroded by the health system weaknesses or contextual challenges.

The second contribution has been to examine the clinical sequelae of the ART regimens in use in the region, describing both novel associations with toxicity and failure to achieve virological suppression, and event rates for common toxicities in a population representative of many contexts where ART is provided in the region.

The coverage of ART in the Western Cape had by 2008 increased to 80% of new AIDS cases each year, and 70% of new patients meeting CD4-based eligibility criteria,[279] and is continually increasing. Determining the population-level impact of this intervention is a research priority. Routine mortality data from registered deaths, examined until 2007, demonstrated that for the three preceding years in the Western Cape, an increase in adult deaths had been averted compared to what would have been expected had coverage not increased.[280] If the increased coverage estimate, coupled with the programme outcomes described in this thesis are robust, a discernible decline in registered adult deaths should be apparent in the next year or two.

Maintaining both the Khayelitsha and Western Cape cohorts going forward is a considerable challenge. Many of the contributions in this thesis relied on the accurate recording in the routine data system of clinical events. As is the case for most academic cohorts in the region, maintaining this level of ascertainment in the context of continued year-on-year increases in patient numbers in unlikely unless there is a

paradigm shift in the conceptualisation of ART research cohorts. The size of cohorts will need to be limited in a way that remains representative, but also allows better clinical record keeping, and accurate data capture and data quality control. This will require increased funding levels, and fewer and smaller cohorts. In South Africa in particular, in addition, there will need to be a greater reliance on data linkage to death registries, laboratory databases, hospital information systems and other disease registries such as the electronic tuberculosis register, in order to assist with near-complete ascertainment of events. These are all approaches which are being pursued in the Western Cape, and it is sincerely hoped that the analyses included in this thesis will be able to be repeated and extended in coming years.

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