535

Clinical Outcomes and Emerging Challenges after 5 years of ART in Khayelitsha, South Africa

Gilles Van Cutsem*[1], Katherine Hilderbrand[1,2], David Coetzee[2,3], Carol Cragg[3], Eric Goemaere[1] & Andrew Boulle[2,3]

1. **Médecins Sans Frontières** South Africa
Ph: +27-21-3645490
Fx: +27-21-3617051
msf.sa@mweb.co.za

2. **University of Cape Town**
School of Public Health and Family Medicine
Ph: +27-21-406-6711
andrew.boulle@uct.ac.za
http://www.ideu.uct.ac.za

3. **Department of Health**
Provincial Government of the Western Cape
Directorate HIV/AIDS and TB
Ph: +27-21-4832518

Setting and background

Khayelitsha is a township in the greater Cape Town area with a population approaching half a million people. The antenatal HIV prevalence rose from 15% in 1999 to 33% in 2005. The tuberculosis (TB) case finding in 2005 was 1,645/100,000. Antiretroviral therapy (ART) has been available in this community since early 2001, making this one of the oldest public sector cohorts in the region.

The first dedicated HIV services were started in Khayelitsha in 1999 with the introduction of prevention of mother-to-child transmission services. In February 2000, Médecins Sans Frontières (MSF), the Western Cape Department of Health, and the University of Cape Town opened three dedicated clinics for the treatment of HIV, introducing ART in May 2001. While smaller numbers of patients were started on ART between 2001 and 2003, enrollment onto ART has been scaled up massively since the Khayelitsha programme was integrated into the national roll-out early in 2004.

The number of people attending voluntary counselling and testing (VCT) increased from 16,000 in 2003 to nearly 27,000 in 2005, among whom 8,676 were HIV positive (33%). In 2005, an average of 720 people were newly diagnosed with HIV each month, while on average 327 new patients were enrolled in HIV clinics. This ongoing increase in HIV testing and the number of people newly diagnosed with HIV has required continuous reinforcement of HIV care capacity at the primary care level. Whilst by early 2006 it was estimated that half of those in need of ART were accessing it in Khayelitsha, the services have subsequently struggled to keep pace with demand due to the increased patient load.

The aim of this study was to describe the clinical and programme outcomes for up to five years on ART, as well as to describe temporal trends in patient enrolment and outcomes.

Methods

Prospective observational cohort study of all treatment-naïve adults started on ART in Khayelitsha since programme initiation in May 2001 until the end of 2005. Follow-up was right-censored at the most recent visit prior to 30 September 2006. Trends in baseline characteristics of patients starting ART are described. Survival, retention in care, and time to starting second-line therapy were modelled using Kaplan-Meier estimates. Viral load suppression to below 400 copies/ml is described at 6-monthly monitoring intervals. Cox proportional hazards regression was used to describe associations with mortality, limited to those patients with an initial CD4 count below 200 cells/µl. Separate models were built for deaths occurring within the first 90 days on ART and for subsequent deaths due to changing hazards over time. Clinical guidelines in use require that a patient have two consecutive viral loads above 5,000 copies/ml prior to regimen switching for failure, and that a structured adherence package be offered after the first raised viral load. The default second-line regimen comprises zidovudine, didanosine and lopinavir/ritonavir.

Baseline cohort characteristics

Table 1: **Patient characteristics at baseline**

	N	Value
Age, median (IQR)	3373	32 (28 - 38)
Female, n (%)	3373	2358 (70%)
Weight, median (IQR), kg	3250	58 (51 - 67)
CD4, median (IQR), cells/µl	3282	87 (35 - 146)
CD4 category, n (%)	3282	
<25 cells/µl		618 (19%)
25 - 50 cells/µl		467 (14%)
50 - 100 cells/µl		743 (23%)
100 - 200 cells/µl		1278 (39%)
>= 200 cells/µl		176 (5%)
Viral load, median (IQR), log10 copies	2945	5.1 (4.6 - 5.6)
Stage (WHO), n (%)	3373	
I & II		348 (10%)
III		1618 (48%)
IV		1406 (42%)
Regimen, n (%)	3373	
AZT/3TC/EFV		456 (14%)
AZT/3TC/NVP		204 (6%)
d4T/3TC/EFV		1,241 (37%)
d4T/3TC/NVP		1,465 (43%)
Other		7 (0%)
Date diagnosed, n (%)	3289	
within 2 years of ART		1,951 (59%)
2 - 5 years previously		1,101 (33%)
>= 5 years previously		237 (7%)
Year starting ART, n(%)	3373	
2001		80 (2%)
2002		204 (6%)
2003		384 (11%)
2004		1,061 (31%)
2005		1,644 (49%)
TB treatment on start, n(%)	3373	1097 (33%)

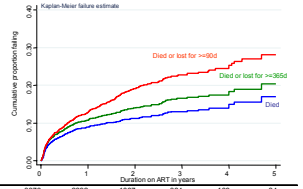
A total of 3373 patients were included in the analysis (Table 1). Median age was 32 years, the median weight was 58 kg and more than two thirds of the patients were women.

A third of the patients started on ART had a CD4 cell count below 50 cells/µl, and 56% in total below 100 cells/µl. Ninety percent of patients started were in WHO stage III or IV.

Prior to the commencement of the national programme in 2004, the starting nucleoside reverse transcriptase inhibitor (NRTI) backbone comprised zidovudine (AZT) and lamivudine (3TC). From late 2003 stavudine (d4T) replaced zidovudine in the default starting regimen, reflected by 80% of patients overall having started on d4T. The proportion of patients started on nevirapine and efavirenz was divided equally.

The vast majority of patients (59%) started ART within 2 years after testing positive for HIV. Whilst only 668 patients were started on ART from 2001 to 2003, the number of new enrollments increased sharply in 2004 with the total patient load at least doubling year on year through the five years. A third of the patients were on treatment for TB at initiation of ART.

Mortality and loss to follow-up



Number in care	3373	2392	1067	384	169	34
Deaths		290	44	14	5	2
Lost to follow-up 365d		66	18	5	0	0
Lost to follow-up 90d		133	83	17	3	2
Percentage dying		8.9%	11.2%	13.0%	14.9%	16.9%
95% confidence interval		(8.0 - 9.9)	(10.1 - 12.4)	(11.6 - 14.6)	(12.8 - 17.4)	(13.6 - 21.0)
Percentage lost to care[1]		10.8%	14.0%	16.6%	18.4%	20.3%
95% confidence interval		(9.8 - 11.9)	(12.8 - 15.4)	(14.9 - 18.4)	(16.2 - 20.9)	(16.9 - 24.3)
Percentage lost to care[2]		12.9%	19.2%	22.8%	25.4%	28.2%
95% confidence interval		(11.7 - 14.0)	(17.7 - 20.8)	(20.2 - 24.8)	(22.6 - 28.1)	(24.5 - 32.3)

1: Definition of lost to follow-up is 365 days; 2: Definition of lost to follow-up is 90d

Figure 1: **Cumulative estimates of mortality and loss to care**

By five years 16.9% (95% CI, 13.6 – 21.0, Figure 1) of patients were known to have died (356 patients in total).

For the purposes of routine reporting, the services use an operational definition of loss to follow-up of 90 days without a visit to the services. Using this definition, the estimate of loss to care is 28.2% (95% CI, 24.5 – 32.3) at five years.

Loss to follow-up in many analyses is however defined as a year without a visit – using this definition, the estimate of loss to care (death or loss to follow-up) at five years is 20.3% (95% CI 16.9 – 24.3).

Although the majority of deaths were in the first year on treatment, deaths continued to be steadily recorded through to five years on ART.

Looking for associations with mortality in multivariate analysis (Table 2), baseline factors signifying disease advancement were predictably associated with early mortality. Patients with a CD4 count below 25 cells/µl had an adjusted hazard ratio (HR) for death of 4.0 compared to those above 100 cells/µl, and those starting with a CD4 count between 25 and 50 cells/µl a HR of 2.7. The association between baseline CD4 count and late deaths was attenuated. Kaposi's sarcoma, other AIDS defining illnesses, and a low initial weight were positively associated with early and late deaths There was little support for associations between mortality and baseline viral load, choice of NRTI, or gender. More recent ART initiation was associated with a lower HR for early deaths (0.8), but not for late deaths.

Unexpectedly, NVP in the initial regimen was negatively associated with early and late deaths (HR 0.5 and 0.7 respectively).

This could possibly be related to indication bias whereby clinicians elect to use EFV in patients they feel are sicker at ART initiation.

There was also an unexpected negative association between being on TB treatment at ART initiation, and late deaths (HR 0.5). It is plausible that in this setting, having TB diagnosed and treated early on could protect against subsequent TB unmasking or re-infection.

Table 2: **Cox models of baseline associations with mortality on ART**

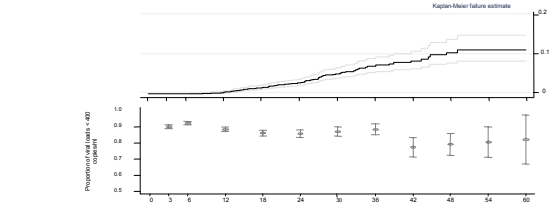
	Early deaths (< 90 days)			Late deaths (>=90 days)		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (per 10 year incr.)	1.1	(0.8 - 1.3)	0.619	1.2	(1.0 - 1.5)	0.033
Male gender	1.0	(0.7 - 1.5)	0.994	1.4	(1.0 - 2.0)	0.045
CD4 count (cells/µl)						
>= 100	Reference			Reference		
50 - 100	1.5	(0.8 - 2.7)	<0.001	1.0	(0.6 - 1.6)	0.017
25 - 50	2.7	(1.5 - 4.9)		1.2	(0.7 - 2.0)	
<25	4.0	(2.3 - 6.8)		1.9	(1.2 - 2.9)	
Log_{10} viral load at start	0.9	(0.7 - 1.2)	0.592	1.2	(0.9 - 1.5)	0.245
AIDS illness besides KS	1.9	(1.3 - 2.9)	0.002	1.5	(1.1 - 2.2)	0.021
Kaposis sarcoma	5.8	(3.1 - 10.8)	<0.001	6.5	(3.6 - 11.8)	<0.001
Weight below 50kg's at start	2.9	(2.0 - 4.2)	<0.001	1.6	(1.1 - 2.3)	0.016
NVP as the NNRTI	0.5	(0.3 - 0.8)	0.005	0.7	(0.5 - 1.0)	0.036
AZT as NRTI	0.7	(0.3 - 1.3)	0.251	1.0	(0.5 - 1.9)	0.890
On TB treatment at start	1.0	(0.7 - 1.5)	0.939	0.5	(0.3 - 0.8)	0.001
Year of ART initiation	0.8	(0.6 - 1.0)	0.048	1.0	(0.8 - 1.3)	0.881

Laboratory outcomes and time to starting second line

Although 7/34 (21%) of the patients who had been on ART for 5 or more years were on second-line regimens by 5 years, the cumulative estimate of switching by 5 years was 11.0% (95% CI 8.2 – 14.7, Figure 3a).

The proportion of patients with viral loads < 400 copies/ml at 1, 2, 3, 4 and 5 years was 88.4%, 85.8%, 88.5%, 79.1%, and 82.1% respectively (Figure 3b). This does not reflect successful suppression in patients on first-line only, as some patients with virological failure were switched to second line regimen and subsequently achieved suppression.

The mean increase in CD4 cell count from baseline at 4 and 5 years on ART was 429 (95 % CI 388 – 469) and 440 (95% CI 341-541) cells/µl respectively.



Patients in care	2997	2392	1613	1067	616	384	245	169	89	34
New on second-line in period	0	10	23	17	19	9	4	4	1	0
Total patients on second-line at duration	0	9	27	31	34	32	29	24	14	7
Cumulative proportion on second-line	0.0%	0.4%	1.5%	2.8%	5.0%	6.9%	8.2%	10.3%	11.0%	11.0%
95% CI		(0.2-0.7)	(1.1-2.1)	(2.1-3.7)	(3.9-6.5)	(5.4-8.9)	(6.3-10.7)	(7.8-13.7)	(8.2-14.7)	(8.2-14.7)
Cross-sectional proportion on second-line	0.0%	0.4%	1.7%	2.9%	5.5%	8.3%	11.8%	14.2%	15.7%	20.6%
95% CI		(0.1-0.8)	(1.0-2.3)	(1.9-3.9)	(3.7-7.4)	(5.6-11.1)	(7.8-16.0)	(9.4-20.2)	(8.3-24.2)	(8.3-34.9)
Viral loads done	2660	2142	1431	931	526	339	190	139	72	28
Percentage eligible tested	88.8%	89.5%	88.7%	87.3%	85.4%	88.3%	77.6%	82.2%	80.9%	82.4%
Proportion viral loads < 400 copies/ml	92.4%	88.4%	86.2%	85.8%	87.1%	88.5%	77.4%	79.1%	80.6%	82.1%
95% CI	(91.3 - 93.3)	(87.2 - 89.7)	(84.3 - 88.0)	(83.4 - 88.0)	(83.9 - 89.8)	(84.6 - 91.7)	(70.8 - 83.1)	(71.4 - 85.6)	(69.5 - 88.9)	(63.1 - 93.2)

Figure 2: **Progression to second-line and overall virological suppression**

Trends over time

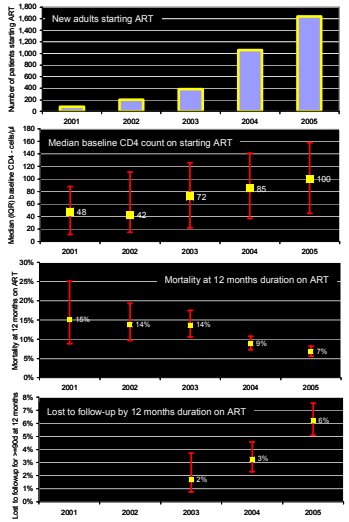


Figure 3: **Temporal trends in enrolment, and 12 month outcomes**

The rapid increase in enrolment (Figure 3a) has been accompanied by an increase in the median CD4 cell count at baseline (Figure 3b). This parameter is a useful measure of the extent to which the programme has been able to catch up with the need for ART. The mortality in the first year has also fallen over the five successive annual cohorts (Figure 3c). It is likely that this is a true reflection of reduced early mortality even though the reduction is offset by an increase in loss to follow-up (based on the operational definition of 90 days without a visit, Figure 3d).

Using this operational definition, two trends are emerging (Figure 4). Firstly, loss to follow-up is occurring earlier, and in greater proportions, for each successive annual cohort of patients starting ART (moving from right to left on Figure 4). Secondly, some of the earlier annual cohorts from which initially very few patients had been lost, have had increases in losses to follow-up over the last 2 years. Whilst it is hoped that not all of these patients are truly lost to the programme, it is a reflection of the challenges facing the clinics in Khayelitsha currently where the rapid increase in patient numbers has outstripped the service's ability to maintain consistent community-based follow-up of defaulting patients. It is also likely that other components of the care and counselling pathways have been compromised by the rapid scaling up of care. Currently the district is exploring new models of care adapted to coping with this increased patient load.

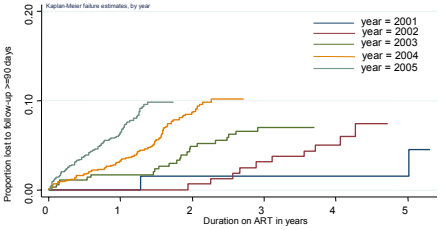


Figure 4: **Proportions of patients lost to follow-up by year of initiation of ART**

Discussion and conclusions

This is one of the first developing country programmes to be able to report on outcomes at 4 and 5 years duration on ART. Whilst there are many service challenges emerging, key findings include:

- Whilst an estimated 16.9% of patients had died by 5 years on treatment, at least 7 out of 10 patients remain alive and in care at this duration.
- A low CD4 count at ART initiation, low initial weight, Kaposi's sarcoma, and other AIDS defining illnesses were most strongly associated with mortality
- One third of patients were on TB treatment when starting ART
- In this setting of extra-ordinarily high TB case-findings, it is possible that being on TB treatment when starting ART could be associated with a modest survival benefit later on by providing cover against subsequent TB unmasking or re-infection
- There was an unexpected statistical association between NVP use as the NNRTI in the initial regimen and improved survival after controlling for measurable confounders

As viral loads have always been available six-monthly in this cohort, virological outcomes could be assessed

- An impressive proportion of patients who were tested maintained viral loads below 400 copies/ml for up to five years on ART
- Cumulatively, 11% of patients were on a second line regimen at 5 years. Looking just at those patients who had been on therapy for a full five years however, 7/34 (20.6%) had been changed to second-line, as had 24/169 (14.2%) of those followed for a full four years

The clinics have rapidly expanded enrolment over the past 4 years. Scaling up access to ART resulted in an increase in the median CD4 count at initiation of ART, and consequently lower early mortality. This scaling up has also however resulted in new challenges:

- Losses to follow-up have increased dramatically since the clinics reached a critical patient load
- These losses include patients who had been on therapy for a few years

Recommendations:

- Scaling up of ART must be accompanied by decentralization of treatment to the most peripheral level and to a greater number of service points in order to avoid the creation of "monster" treatment sites where adequate follow-up cannot be maintained.
- Appropriate systems need to be created to accommodate the ever-increasing patient load. This includes capacitating all levels of health care workers (in the South African settings especially nurses) to deliver and monitor ART, and ensuring additional adherence support by non-medical staff.