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Determinants of survival in AIDS patients on antiretroviral therapy in a rural centre in the Far-North Province, Cameroon

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Summary

OBJECTIVE To analyse the outcomes of antiretroviral therapy (ART) in routine conditions in a rural hospital in the Far-North province of Cameroon. METHOD Retrospective cohort study of 1187 patients >15 years who started ART between July 2001

and December 2006. The survival time was estimated by Kaplan–Meier analysis and Cox proportional hazard models were fitted to explain survival.

RESULTS Upon enrolment, 90.4% patients were in WHO stage III or IV and 56.1% had a BMI <18.5. Median CD4 count was 105 cells/mm³ (IQR 40–173). At the end of the study period, 338/1187 had died and 59/1187 were lost to follow-up. The survival probability was 77% at 1 year [95% CI: 75–80] and 47% at 5 years [95% CI: 40–55]. The median survival time was 58 months. CD4 count, haemoglobin, BMI, sex and clinical stage at enrolment were independent predictors of mortality. CONCLUSION This study confirms the clinical benefit of ART programs in a remote and resource-constrained setting operating in routine conditions. The challenge ahead is to secure earlier access to ART and to maintain its longer-term benefit.

keywords antiretroviral therapy, Africa, HIV/AIDS, treatment, survival analysis

Introduction

Roughly 75% of AIDS patients in need of antiretroviral therapy (ART) in the world still have no access, and most of them live in Africa (World Health Organization 2006). This, despite the fact that the three by five initiative of the World Health Organization (WHO), as well as the resources provided by the Global Fund, greatly facilitated access to ART in all regions of the world and boosted ART programs in most of sub-Saharan Africa, where the number of persons treated was multiplied by more than eight in just 2 years [World Health Organization (WHO) 2006].

The clinical benefit of ART for AIDS patients, in terms of mortality reduction and improved quality of life, is well established but shows regional variations, with higher case fatality rates in poor countries (Braitstein *et al.* 2006; Egger 2007). There are several predictors of mortality for patients on ART: viral load, CD4 count, total lymphocytes, body mass index (BMI), and adherence. Although these determinants tend to be similar across the world, there are some striking differences in their relative frequency, e.g. the much lower baseline CD4 counts of patients starting ART in poor countries (Egger 2007). The evidence on ART outcomes in sub-Saharan Africa mostly stems from research or pilot projects supported by international agencies (Laurent *et al.* 2005b) depicting efficacy rather than effectiveness. Data on effectiveness, i.e. when ART is delivered in the routine operating conditions of hospitals with limited resources, are rare and often restricted by a small number of patients and/or short follow-up periods (Coetzee *et al.* 2004a; Akileswaran *et al.* 2005; Laurent *et al.* 2005b). The question of ART effectiveness in real-life conditions still needs attention. Several authors have evoked the constraints faced, such as weak health systems and poor accessibility to health services (Bekker *et al.* 2003; Kabugo *et al.* 2005; Stevens *et al.* 2005; Organisation Mondiale de la Santé & ONUSIDA 2006).

In Cameroon, the fight against HIV/AIDS is a priority since the launch of an HIV prevention programme early 2000. The HIV/AIDS control strategy 2006–2010 has three major objectives: preventing new HIV-infections, promoting universal access to AIDS care and reducing the impact of HIV/AIDS on children. ART care is provided at all levels of the health system and is mainly financed by the government (40%) and through the Global Fund (more than 50% since 2005). So far, the only clinical studies to

evaluate the efficacy of ART in Cameroon were conducted in Douala and Yaoundé, two major cities located in the wealthier part of the country (Laurent *et al.* 2004, 2005b, 2006, 2007; Bourgeois *et al.* 2005). The objective of our work was to document the outcome of ART in terms of survival and its determinants when provided in the rural and resource-constrained context of the Far-North Province of Cameroon.

Methods

Context

The Far-North Province of Cameroon (*la Province de l'Extrème-Nord*) extends over 34 246 km² and has a population of 3 551 944 inhabitants belonging to more than 50 ethnic groups. In 2004, HIV prevalence in this province was estimated at 2% in the population aged 15–49 years (Mosoko & Affana 2005).

AIDS care in Cameroon is regulated by the government: ART has to be provided in specialized centres with an official accreditation: a Centre de Traitement Agrée [Approved Treatment Centre (ATC)] or reference centre, or an Unité de Prise en Charge [Treatment Unit (TU)], a decentralized structure. The Far-North province has two ATCs and, since the end of 2005, six TUs. The ATC of Petté is operated by the rural district hospital of Petté. This 160-bed private not-for-profit hospital was created in 1968 by a Swiss charity, Fondation Sociale du Nord-Cameroun, and is supported by the Swiss Development Cooperation and private donors. No earmarked funding for AIDS is received from international donors. Petté Hospital started the provision of ART in 2001 and was accredited as ATC in March 2002. For many years it was the only centre in the province offering comprehensive HIV/AIDS care. It is noteworthy that all services provided by the ATC of Petté are integrated in the regular hospital activities, i.e. there is no separate outpatient clinic or ward for HIV/AIDS patients. Every patient found HIV-positive is screened for opportunistic infections and staged according to the WHO criteria. Patients with CD4 count <200 cells/mm³ and/or WHO stage III/IV are eligible for ART. The others are monitored closely and started on ART as soon as eligible. HIV test results are delivered the same day, and CD4 results overnight. As soon as all test results are available, eligible patients are started on ART. The patient circuit is kept as short as possible and there was no waiting list of patients to be started on ART during the study period.

AIDS care at Petté includes management of opportunistic infections as well as first-line drugs (initially at 15 000 CFA (22 ϵ /month) but since 2005 reduced to 3000 CFA or 4.5 ϵ per month). Second-line ART was provided at 7000 CFA or 11.5 € per month. Prices mentioned are the subsidized prices patients have to pay out-of-pocket, though there is a mechanism to waive the fee partially or totally for those who cannot afford to pay. The ART protocols are standardized and in accordance with the WHO recommendations (WHO 2003). The first line is one of the four following combinations: AZT + 3TC + NVP (Duovir® + Névumune®), AZT + 3TC + EFV (Duovir® + Stocrin®), D4T + 3TC + NVP (Triomune®), D4T + 3TC + EFV (Lamivir-S® + Stocrin®), with an estimated 70% of regimens being the fixed-dose combination Triomune®. The second line consists of 2 NRTI + IDV, with DDI (Videx®) as the most commonly used NRTI. All patients with CD4 <350 cells/mm³ receive cotrimoxazol prophylaxis.

At the start of ART, every patient benefits from adherence counselling. Every patient has to bring along a relative who is trained to support the patient in complying with treatment. Non-adherent patients are referred to special counselling sessions. Defaulters are actively traced by a messenger or by telephone.

The first follow-up visit is scheduled after 15 days, and on a monthly basis thereafter. CD4 monitoring is done on day 15, day 45, month 6 and every 6 months thereafter. The cost of this test decreased from an initial US\$ 30 to US\$ 20 in 2002 and to US\$ 6 in 2006. Therapeutic failure was determined clinically and immunologically according to the 2003 WHO criteria (WHO 2003).

Patients

All patients older than 15 years who were naïve to any antiretroviral therapy, and started ART between 1 July 2001 and 31 December 2006 at the ATC of Petté were eligible for this retrospective study. Patients who did not return for follow-up visits for more than 3 months were considered lost to follow-up. An intensive tracing effort by the ART centre in 2006 allowed updating the information on survival time and outcomes in many of those lost to follow-up. If they had died at home, they were categorized in the data analysis as having died immediately after the last registered follow-up visit, as for most of them the exact time of death was impossible to determine. A follow-up visit was considered 'on time' if it was not more than 3 days later than the date of appointment. If later, it was considered 'late' and if patient attended earlier than the appointment date, it was considered 'not scheduled'.

Data analysis

Since the start of the ART program in Petté, all patient data have been entered on a daily basis in an ACCESS database

developed by EPICENTRE (Fuchia version 1.4.). A survival analysis was carried out where death from all causes was considered as event of interest. The survival time of patients still alive on 30 June 2007 and of those referred to other facilities (further called transferred out) was censored. As the group 'lost-to-follow-up' may be more at risk of death than the others, a sensitivity analysis called 'the worst-case scenario' was carried out, in which all dropouts were classified as 'deceased' immediately after their last contact with the centre. Survival time was estimated by Kaplan-Meier curves. Survival curves for subgroups were compared by the logrank test. Cox proportional hazards models were fitted to identify independent determinants of survival. A number of possible predictors of mortality were unavailable for a significant proportion of patients. We explored the influence of these missing data using two approaches: (i) including 'Unknown' as a separate category in the model (Table 3) and (ii) adding those with unknown predictor to the reference category (data not shown). Results were similar for both approaches. Changes in CD4 count and weight were summarized using mean and median changes from baseline and 95% confidence intervals (CIs) and tested using the Wilcoxon signed rank test. The CIs were calculated using the normal approximation with 1.58* interquartile (IQR) range as standard deviation of the median. The analysis was carried out with the software STATA (version 9.0; StataCorp., 4905 Lakeway Drives, College Station, TX 77845, USA).

Ethical clearance for the study was obtained from the National Ethical Committee of Cameroon.

Results

During the study period, 2161 HIV-positive persons were followed at the ATC in Petté. Between July 2001 and December 2006, 1279 patients were started on ART. We included 1187 treatment naïve patients over 15 years old in the analysis, who had at least one follow-up visit after the start of ART. Median age was 35 years (IQR 29-41) and 55.6% of patients were male. Out of 1187 patients, 1073 (90.4%) were started on ART at an advanced stage of the disease (WHO stage III or IV) (Table 1). The main opportunistic infections observed during the initial visit (i.e. first contact with centre) were tuberculosis, pneumonia and skin infections. This spectrum remained stable over time (data not shown). Median CD4 count at ART initiation was 105 cells/mm3 (IQR 40-173) and 306 (25.8%) patients had a CD4 count \leq 50 cells/mm³. Fiftysix per cent of patients had a BMI ≤ 18.5 kg/m². Table 2 shows how median CD4 count at initiation evolved by year of enrolment: no substantial increase over time was observed.

Of the 1187 patients followed, 570 (48.0%) were still under follow-up on 30 June 2007, 59 (5.0%) were lost to follow-up, 338 (28.5%) had died and 220 (18.5%) were transferred out. Total mortality rate over the study period was 20.2 per 100 person-years at risk (338/1677 personyears). In the worst-case scenario, considering all those lost to follow-up as deceased immediately after the last date of contact, mortality rate was estimated at 23.1 per 100 person-years at risk. The median survival time was 58 months (49 months in the worst-case scenario). The

Table 1 Characteristics of patients upon initiation of antiretro-viral therapy at the ATC of Petté, Cameroon (July 2001–December2006)

Variables	Number ($n = 1187$)	Percentage
Sex		
Male	660	55.6
Female	527	44.4
Clinical stage		
III or IV	1073	90.4
I or II	114	9.6
Civil status		
Single	121	10.2
Divorced or widowed	320	27.0
Married monogamous	505	42.5
Married polygamous	241	20.3
Occupation		
Petty trader	165	13.9
Farmer	117	9.9
Civil servant	150	12.6
Other	299	25.2
No	456	38.4
Residence		
Cameroon		
Far-north Province	1059	89.2
Other	66	5.6
Other country	62	5.2
CD4		
Not available	126	10.6
<50	306	25.8
≥50	755	63.6
Treatment regimen		
First-line	1159	97.6
Second-line	14	1.2
Bitherapy	14	1.2
BMI		
Unknown	77	6.5
≤18.5	666	56.1
>18.5	444	37.4
Year of ART start		
Before 2003	270	22.7
2003	231	19.5
2004	287	24.2
2005	251	21.1
2006	148	12.5

Table 2 Median CD4 count at initiation of therapy by year of ART start

Year	Number of patients starting ART*	Median CD4 at initiation (cells/mm ³)	IQR
2002	175	105	41-184
2003	221	115	42-195
2004	280	94.5	30-160.5
2005	242	104	52-170
2006	143	115	42–167

ART, antiretroviral therapy.

*Initial CD4 count missing for 126 patients.

survival probability at 1 year was 77% (95% CI: 75-80) and at 5 years 47% (95% CI: 40-55) [Worst case 65% at 1 year (95% CI: 62-68) and 40% at 5 years (95% CI: 33-46)]. Figure 1 shows two phases: an early phase with a mortality risk of 20% in the 6 first months of treatment (mortality rate of 52 per 100 person-years at risk), after which the mortality stabilizes at a lower level with a mortality rate of approximately 10 per 100 person-years at risk. An increase in mortality risk was observed in the 5th year of follow-up, but due to the small number (91) of patients in follow-up for more than 4 years this trend may be due to chance. During the study period, the hospital of Petté carried out 12 801 outpatient consultations for patients on ART, and 71.4% of these (9140/12 801) were scheduled. However, the proportion of patients appearing for their appointments was small in 2001 (49.1%) and increased gradually to 67% in 2006.

The median CD4 cell count at the start of ART was 105 cells/mm³ and increased significantly over 5 years of follow-up ($P \le 0.001$). The median gain in CD4 compared to baseline was 136 cells/mm³ at 6 months, 150 cells/mm³ at 12 months and 181 cells/mm³ at



Figure I Survival of patients on ART at the Petté hospital (July 2001–December 2006).



Figure 2 Evolution of CD4 in patients on ART at the Petté ATC (July 2001–December 2006).

24 months (Figure 2). At all timepoints there was a significant increase in weight compared to baseline ($P \le 0.010$), with an average weight gain at month 12 of 6.3 kg.

In univariate analysis (not shown), patient survival under ART was significantly associated with clinical AIDS stage at start, baseline CD4 count, haemoglobin and lymphocyte count, with baseline BMI, sex, and % of visits on time while TB at initiation was not. In multivariate analysis, only baseline CD4, sex, BMI, baseline haemoglobin and WHO clinical stage remained significantly associated with survival (Table 3). Percentage of visits on time was eliminated from the model because data were missing for more than 20% of patients. Patients with a baseline CD4

Table 3 Determinants of mortality in patients on ART in ATC ofPetté, Cameroon (July 2001–June 2007)

	Hazard ratio	P-value
Sex (M/F)	1.73 (1.37-2.19)	< 0.001
WHO stage		
I or II	1	< 0.001
III	2.02 (1.11-3.67)	
IV	3.79 (2.06-6.97)	
CD4	× ,	
Not available	0.66 (0.43-1.02)	< 0.001
≤50	1.85 (1.46-2.55)	
>50	1	
BMI		
Not available	6.53 (4.42-9.67)	< 0.001
≤15	3.01 (2.16-4.19)	
15-18.5	1.57 (1.16-2.13)	
>18.5	1	
Haemoglobin		
Not available	1.33 (1.02-1.74)	0.002
≤8.5	1.93 (1.36-2.76)	
>8.5	1	

ART, antiretroviral therapy; ATC, Approved Treatment Centre.

count \leq 50 cells/mm³ presented a mortality risk twice as high as those with >50 cells/mm³ (HR 1.85). A BMI between 15 and 18.5 kg/m² was related to a 1.5 times higher risk of death than a BMI >18.5 kg/m² (HR = 1.57). This risk rose to three times more for those with a BMI \leq 15 kg/m². Patients in stage III and IV were two to four times more likely to die than patients in stage I and II. Men were at nearly twice the risk of death as women (HR = 1.7). Patients with haemoglobin \leq 8.5 g/dl had two times more risk of death than those with a haemoglobin rate >8.5 g/dl (Table 3).

The drug regimen was changed for 40 patients because of severe side effects (29) or because of therapeutic failure (11). All failures were followed up after month 12 of treatment. Close to 45% (13/29) of side effects arose after the 12th month, these were mainly peripheral neuropathy and lipodystrophy, attributable to D4T.

Discussion

This 5-year retrospective cohort study of AIDS patients on ART gives an insight in survival and its determinants in a rural hospital setting in Cameroon. The spectrum of patients enrolled in this centre was similar for many other start-up ART programs in resource poor settings. More than half of the patients were severely malnourished at baseline, and a very high proportion (26%) of them were in severe immune depression (CD4 count \leq 50 cells/mm³). Strikingly, the latter proportion stayed high, and above 18%, for each single year of the study period, implying that over time, patients did not get earlier access to ART. In our rural context, late uptake of Voluntary Counselling and Testing (VCT) services as well as the stigmatization and denial surrounding HIV/AIDS continues to lead to very late initiation of ART. It remains a challenge for integrated health services such as those provided at Petté, to stimulate earlier VCT uptake through the various entry points in the health system.

Table 4 shows how results in Petté were somewhat inferior to those obtained in other resource-constrained settings (Laurent *et al.* 2002; Tassie *et al.* 2003; Coetzee *et al.* 2004a Laurent *et al.* 2004; Severe *et al.* 2005; Djomand *et al.* 2003). In Petté, we observed a very important early mortality. Between 1 and 4 years on ART, the mortality risk was less pronounced, but appeared to increase again after 4 years, though the confidence interval around the survival probability at 5 years is very wide. A lot of factors could have contributed to the early mortality in our cohort, most importantly the fact that the majority of patients started ART in an advanced stage of the disease, and that this proportion apparently did not diminish over time.

			-] //			-				
		6 mo:	nths	12 m	onths	24 months	36 mo	nths 4	+8 months	60 months
Ref. Country	и	и	% (95% CI)	и	% (95% CI)	n % (95% CI)	% и	6 (95% CI) 1	1 % (95% CI)	<i>n</i> % (95% CI)
This study Camero	on 118	37 723	80.0 (77.0-82.0)	578	77.0 (75.0-80.0)	351 71.0 (66.0–74.0)	181 6	2.0 2.0	1 58.0 (53.0-62.0)	13 47.0
Laurent <i>et al.</i> 2004 Camero	9 uc	50 50	85.0 (73.0-92.0)	I	I	1	<u>,</u> 1			
Coetzee et al. 2004a South-A	frica 28	37 251	88.1 (88.8-90.1)	168	86.3 (81.7-89.8)	34 86.3 (81.7-89.8)	I	I	I	I
Djomand et al. 2003 Ivory Co	bast 27	- 92	I	n.m.	84.0 (80.0-89.0)		I	I	I	I
Laurent et al. 2002 Senegal	5	58 n.n	n 94.8 (84.6-98.3)	n.m.	85.0 (72.2-92.2)	I	I	I	I	I
Severe et al. 2005 Haïti	91	10 n.n	n 90.0 (n.m.)	n.m.	87.0 (n.m.)	I	I	I	I	I
Kheang 2006 Camboc	lia 110)2 n.n	n 95.0 (n.m.)	n.m.	92.1 (n.m.)	n.m 87.1 (n.m.)	I	I	I	I
Site1										
Site 2	120)4 n.n	n 92.1 (n.m.)	n.m.	90.6 (n.m.)	n.m 88.4 (n.m.)	I	I	I	1
Tassie et al. 2003 Multi-cc	untry 74	13 n.n	n. 89.9 (86.8-92.1)	I	I	1	I	I	1	I
Ferradini et al. 2007 Camboc	lia 41	16		n.m	87.0 (83.0-90.0)	350 85.0 (81.0-880)				

Table 4 Comparison of survival probability on ART in several studies

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The high mortality after 4 years on therapy is a finding that remains to be confirmed on a larger number of patients, and could be possibly related to undiagnosed treatment failure. In Cameroon, genotypic resistance to first line ART occurred at a rate of 3.2 to 7.1 per 100 person-years (95% CI 1.8-28.4) in Douala (Bourgeois et al. 2005; Laurent et al. 2006) and 16.4% in Yaounde (Laurent et al. 2006). In Senegal, this resistance was observed in 12.5% of patients (Laurent et al. 2005a) while in Germany and Luxemburg, Van Vaerenbergh et al. (2002) observed 28% of resistance. In our setting, resistance was suspected in every patient presenting treatment failure (as defined by the WHO 2003 clinical and immunological criteria) for whom an adherence problem could be ruled out. A regimen switch to second line because of suspected resistance was reported in 11 patients (0.9%), or a rate of 0.6 for 100 person-years, a rate well inferior to other reports and most likely therapeutic failures were under-diagnosed in the cohort at Petté.

Risk of death was two to four times higher for patients with clinical AIDS at the start of ART. Mortality was roughly two times higher for patients who began ART with a severe immune-depression (CD4 <50 cell/ml). These results are similar to those described elsewhere (Hogg et al. 1999; Grabar et al. 2000; Weidle et al. 2002; Bekker et al. 2003; Coetzee et al. 2004a; Dabis et al. 2005; Ivers et al. 2005; Kabugo et al. 2005; Laurent et al. 2005b; Sterne et al. 2005; Crum et al. 2006; Etard et al. 2006; Kheang 2006; Egger 2007). Despite the fact that more than 90% of the patients started ART in an advanced clinical stage, the gains in CD4 count and weight were impressive. These results are comparable to other reports from Cameroon (Laurent et al. 2004, 2005b, 2006, 2007; Bourgeois et al. 2005) and elsewhere (Bekker et al. 2003; Coetzee et al. 2004a; Dabis et al. 2005; Ivers et al. 2005; Kheang 2006; Weidle et al. 2006). Patients with a BMI <15 kg/m² were at higher risk of death, a result also reported from Senegal, Cambodia and Malawi (Etard et al. 2006; Kheang 2006; Zachariah et al. 2006). In 2004, a clinical trial conducted by Fawzi et al. 2004 documented the harmful role malnutrition plays in the clinical progression of AIDS in resource-poor settings. Considering the fact that 56.1% of our patients were malnourished at enrolment, strategies for nutritional rehabilitation should be adopted in ART care.

Male sex was a predictor of mortality with a risk almost double that of female sex (HR 1.73; 1.37–2.19). Several authors described gender differences in ART outcomes (Sterling *et al.* 2001; Moore *et al.* 2002; Kremer & Sonnenberg-Schwan 2003; Perez-Hoyos *et al.* 2003), while others found none (Egger *et al.* 2002; Bourgeois *et al.* 2005; Nicastri *et al.* 2005; Braitstein *et al.* 2006; Etard *et al.* 2006; Zachariah *et al.* 2006). Potential confounders as gender differences in treatment adherence, risk behaviour and financial accessibility could offer alternative explanations for such an association.

The proportion of loss to follow-up in this cohort was small (thanks to a tracing effort in 2006) and comparable to other data from the African region (Grabar et al. 2000; Bekker et al. 2003; Coetzee et al. 2004a; Bourgeois et al. 2005; Lawn et al. 2005; Etard et al. 2006; Zachariah et al. 2006). Very recently, a systematic review by Rosen et al. (2007) of clinical outcomes in 33 ART cohorts in 13 African countries showed that reported mortality rates were inversely correlated to the proportion of loss to follow-up. This is corroborated in our cohort, as 5% of loss to follow but 20% overall mortality was found. The opening of six treatment units in the province end of 2005 and subsequent referral to a centre closer to home led to loss of information about a substantial number of patients in the last year of the cohort. If we assume that those remained alive and on therapy, the overall proportion of patient retention in the ART cohort was 66.55% and this compares favourably to the average of 60% observed during a 24 months follow-up in the programs mentioned above (Rosen et al. 2007).

Our study cohort has a rather long observation period (>5 years) and reflects the operational realities of a busy district hospital where ART care is fully integrated with other clinical activities. These features contain at the same time the strengths and the weaknesses of this study. We were not able to determine the exact cause of the deaths, and to attribute them all to HIV overestimates the AIDS-related mortality rate. The data were collected retrospectively from patient files in a context of routine care and hence there might be a certain degree of underreporting of events. After the intensive tracing and home visiting of defaulters was conducted in 2006, the remaining number of 'loss to follow-up' in the database was low, but they were less likely to survive than the others as judged from their prognostic markers at baseline. Therefore, we evoked an extreme scenario in the data analysis considering that all defaulters had died immediately after their last visit to the centre. This worst-case scenario is probably over-estimating the true mortality risk, as in AIDS patients not on ART only 25-50% will have died after 1 year (Schneider et al. 2004). Lastly, our estimation of survival time at 5 years was not very precise, and missing data prevented us from analysing the role of adherence on survival time, though several studies report this as an important determinant (Laniece et al. 2003; Coetzee et al. 2004b; Mannheimer et al. 2006; Robbins et al. 2007), especially when ART is not provided for free (Crane et al. 2006; Oyugi et al. 2007).

The clinical outcomes of AIDS patients on ART in routine hospital practice in the Far-North Province of Cameroon are slightly inferior to those observed in research projects in other regions of sub-Saharan Africa. We noted an important early mortality as well as a trend to rising mortality after 4 years. The factors associated with survival were: baseline CD4 count, basic haemoglobin, BMI, clinical stage and sex. Our study, while confirming the clinical benefit of ART in rural areas of Africa, raises the challenge of earlier and timelier access to ART and that of maintaining this clinical benefit over time.

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