Improved Survival and Antiretroviral Treatment Outcomes in Adults Receiving Community-Based Adherence Support: 5-Year Results From a Multicentre Cohort Study in South Africa

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Introduction: A large increase in lay health care workers has occurred in response to shortages of professional health care staff in sub-Saharan African antiretroviral treatment (ART) programs. However, little effectiveness data of the large-scale implementation of these programs is available. We evaluated the effect of a community-based adherence-support (CBAS) program on ART outcomes across 57 South African sites.

Methods: CBAS workers provide adherence and psychosocial support for patients and undertake home visits to address household challenges affecting adherence. An observational multicohort study of adults enrolling for ART between 2004 and 2010 was performed. Mortality, loss to follow-up, and virological suppression were compared by intention to treat between patients who received and did not receive CBAS until 5 years of ART, using multiple imputation of missing covariate values.

Results: Of the 66,953 patients who were included, 19,668 (29.4%) patients received CBAS and 47,285 (70.6%) patients did not. Complete-case covariate data were available for 54.3% patients. After 5 years, patient retention was 79.1% [95% confidence interval (CI): 77.7% to 80.4%] in CBAS patients versus 73.6% (95% CI: 72.6% to 74.5%) in non-CBAS patients; crude hazard ratio (HR) for attrition was 0.68 (95% CI: 0.65 to 0.72). Mortality and loss to follow-up were independently lower in CBAS patients, adjusted HR (aHR) was 0.65 (95% CI: 0.59 to 0.72) and 0.63 (95% CI: 0.59 to 0.68), respectively. After 6 months of ART, virological suppression was 76.6% (95% CI: 75.8% to 77.5%) in CBAS patients versus 72% (95% CI: 71.3% to 72.5%) in non-CBAS patients ($P < 0.0001$), adjusted odds ratio was 1.22 (95% CI: 1.14 to 1.30). Improvement in virological suppression occurred progressively for longer durations of ART [adjusted odds ratio was 2.66 (95% CI: 1.61 to 4.40) by 5 years].

Conclusions: Patients receiving CBAS had considerably better ART outcomes. Further scale-up of these programs should be considered in low-income settings.

Key Words: antiretroviral treatment, community-based adherence support, outcomes, South Africa, resource-limited settings, health workers

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INTRODUCTION

In patients on antiretroviral treatment (ART), adherence is a critical predictor of HIV viral suppression, disease progression, and mortality.[1,2] In sub-Saharan Africa, ART adherence has been equal or superior to adherence in developed countries.[3] However, adherence tends to wane with increasing duration of treatment, and sustained efforts to ensure high levels of long-term adherence to ART are vital.[1] As sub-Saharan African ART program patient numbers have expanded, increasing patient attrition has occurred[4–6] and higher levels of virologic failure and drug resistant mutations have been reported.[5,7] There is a severe shortage of professional health workers in sub-Saharan African countries.[8–11] As a response to this, the number of lay health workers in ART programs has been substantially increased during the last half-decade,[12,13] and there have been calls to further strengthen community-based adherence support (CBAS) initiatives for patients receiving ART.[14,15] To justify further resource allocation to such interventions, evidence of their effectiveness is required.

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CBAS has been associated with reduced mortality and loss to follow-up (LTFU) and with improved virological outcomes in low-income settings.[16–19] Limitations of these studies, however, include small sample size,[16] lack of adjustment for potential confounding,[17,20] and control arm contamination,[21] and these studies followed patients for a maximum of 26 months. Data is not yet available on the long-term effectiveness of large-scale implementation of CBAS programs for ART patients in low-income settings.

The aim of this study was to assess the effectiveness of a large CBAS program for ART patients enrolled between 2004 and 2010 in 4 South African provinces. Clinical, virological, and immunological outcomes after starting ART were compared between patients who received and did not receive CBAS at government-sector ART facilities using routinely collected data.

METHODS

Study Design and Setting

A multicentre cohort study of adults starting ART was conducted at 57 public health care facilities supported by Kheth'Impilo (previously Absolute Return for Kids), a South African nongovernmental organization (NGO). The government-implemented rollout of ART, initiated in 2004, follows the public health approach of the World Health Organization (WHO) with the provision of standardized first- and second-line regimens. At the end of 2010, almost 1.4 million South Africans had been initiated on ART in the public sector, with ART coverage being 55%.[22] Kheth'Impilo provides clinical staff, infrastructure, capacity development, and electronic data collection systems and uses a CBAS program using patient advocates (PAs). PAs are lay community health workers who provide adherence and psychosocial support for ART patients, and undertake home visits to ascertain and address household challenges potentially impacting on adherence. PA support starts from the time of pre-ART preparation and continues throughout long-term patient care.

PAs are community members chosen through a transparent process involving community representatives, clinic staff members, and NGO line managers. PAs are generally unemployed before working as a PA, and positions for PAs are advertised in local media. They have to have completed high school, be numerate and literate in English, be fluent in the local language, and have good community standing. They are trained (in a 3-week intensive course) regarding HIV and tuberculosis (TB) infection and treatment, including psychosocial issues impacting on adherence and how to address these. PAs receive a 5-day refresher course a year after starting and monthly 1-day training and debriefing workshops.

During a patient's initial home assessment by a PA, family and other household members are also evaluated. Issues assessed using a standardized form (see **Supplemental Digital Content 1**, http://links.lww.com/QAI/A348) include TB and HIV testing status of the household, nutrition security, substance abuse, domestic violence, nondisclosure, current household recipients, those eligible to receive government social grants (as poverty relief), and vital documentation, including birth certification. All psychosocial issues are discussed at clinic multidisciplinary team meetings (comprising doctors, nurses, clinic adherence counselors, PAs, and social workers), and interventions agreed by the team are implemented by the PA or social worker. PAs also offer group educational sessions to all patients at the clinic about HIV/TB, the importance of adherence, and nutrition.

After the psychosocial screening visit, home visits occur weekly for a month. PAs supervise taking of medication, advise on medication storage, do adherence checks using self-reported adherence, and, in certain situations, ART pill counts. They provide one-on-one counseling with patients regarding adherence and psychosocial problems and follow-up on progress made regarding referrals to social workers. Health promotion education, symptom screening for TB, and other opportunistic infections are performed, with referral to clinics if indicated. Patients who are clinically ill, pregnant, or are on TB treatment are regarded as "'very important patients," and subsequent visit frequency remains high, being at least monthly. Stable patients are visited on at least a 3-monthly basis. If clinic visits are delayed, frequency of home visit increases. Site-based patient facilitators link patients to PAs, and community-based area coordinators manage approximately 20 PAs each in the community. Each PA is assigned 80–120 ART patients and tracks patients with a paper diary. Visit details, including interventions, are recorded and captured electronically by site-based data capturers.

Patients from all NGO-supported ART sites at which PAs were active that had electronic clinical data collection systems were eligible for inclusion during the study period. Facilities are distributed across 4 provinces (Western Cape, KwaZulu-Natal, Eastern Cape, and Mpumalanga) and included hospitals and primary health care (PHC) clinics in urban and rural areas.

Adults with CD4 cell counts <200 cells/μL and/or a WHO stage IV defining illness were eligible to start treatment as per the 2004 South African national treatment guidelines.[23] From April 2010, ART eligibility criteria were expanded to include adults who were pregnant or diagnosed with active TB with CD4 cell counts ≤ 350 cells/μL.[24] Standardized first-line regimens consisted of 2 nucleoside reverse transcriptase inhibitors and 1 nonnucleoside reverse transcriptase inhibitor. Fixed-dose combinations were not used (except for combined zidovudine/lamivudine).

All adults (16 years of age or older) not previously enrolled for ART, starting triple-drug combination ART between January 1, 2004 and September 30, 2010, with documented date of birth, gender, and date of starting ART, who initiated ART at least 6 months before site database closure, who had at least one day of follow-up time on ART, and in whom it was documented whether the patient received CBAS support from the start of ART were included in analyses. Patients were followed up from the start of ART until the earliest of last clinic follow-up visit (for patients dying, transferring out, or LTFU), 5 years from starting ART, NGO exit from a site (7 sites), or March 31, 2011.

Patients were allocated to receive CBAS during the pretreatment preparation period by the community area

coordinator if a PA was active in the area of the patient's home, PA capacity was available, and patient consent was obtained. As the development of the CBAS program at individual sites was progressive, few patients were initially allocated to PAs, but this increased as the program expanded. Clinical and socioeconomic criteria were not used in deciding the initial allocation status of patients to receive CBAS (although clinical severity would affect subsequent visit frequency of CBAS patients). For analyses, patients were assigned to the CBAS group if allocated to receive support from a named PA since the start of ART. All patients (CBAS and non-CBAS) received 3 group training sessions regarding HIV education and adherence before starting ART. Certain clinics had site-based adherence counselors who provided individual and/or group adherence counseling to both CBAS and non-CBAS patients referred to them by clinical staff if there were concerns about nonadherence.

Analyses were by intention to treat (ITT), ignoring subsequent changes in exposure status. Outcome measures were death, LTFU, virological suppression (VS), and changes in CD4 cell count after starting ART. Patient attrition was defined as a combined endpoint of mortality or LTFU. A patient was defined as LTFU if no visits to the clinic occurred for 180 days or more.[25] Patients who did not receive CBAS and who missed appointments would be traced by telephone or where available, a district tracing team would visit the home. CD4 cell count was measured at ART initiation and at 6-monthly intervals, and viral load was measured 6 monthly on treatment. Virological suppression was defined as a viral load <400 copies/mL. Laboratory measurements were performed by the South African National Health Laboratory Service.

Data Collection and Statistical Analyses

Individual-level patient data were collected prospectively for routine monitoring purposes by designated site-based data capturers at each patient visit using standardized custom-designed databases, which were pooled to a central data warehouse using standard operating procedures. The site databases were designed by the NGO using Microsoft Access and were used for routine clinical data collection and patient and clinic management. Regular data cleaning and quality control procedures were implemented.

Baseline characteristics between groups were compared with relative risks (RRs) and 95% confidence intervals (CIs). Kaplan–Meier estimates were used to calculate crude estimates of time to death or LTFU from starting ART. The log-rank test was used to compare groups.

Multivariable Cox proportional hazards models were used to analyze the association of CBAS with mortality and LTFU. All models were adjusted for gender, age, baseline CD4 cell count, and additional a priori specified baseline patient and site-related covariates that were plausible confounders, which produced a variation in the point estimate. Additionally, models were controlled for unmeasured heterogeneity between site cohorts. To avoid potential bias from excluding patients with missing covariate values, multiple imputation of missing values by chained equations were performed using 10 imputed data sets.[26] Multivariable analyses were run on each of the data sets that included the imputed values, and the results combined using Rubin rules.[27] As a sensitivity analysis, models were also run using a complete-subjects approach (including only subjects with all data for all variables). Modification of the effect of CBAS on mortality and LTFU was assessed by stratifying effect measures by plausible modifiers. The number needed to treat (NNT) to prevent a case of death or LTFU was calculated as appropriate for time-to-event outcomes.[28]

Virological outcomes were analyzed primarily by ITT,[29] including all patients in the denominator for each group as allocated but censoring observations for patients in care with missing viral load results at that time point. Log-binomial regression with generalized estimating equations was used to calculate crude associations of CBAS with virologic suppression between months 6 and 60 after starting ART, using robust variance estimates.[30] For multivariable analyses using the imputed data sets, a logit link function was used to estimate adjusted odds ratios (aORs). Additionally, estimates were calculated for each 6-monthly measurement interval. A sensitivity analysis was conducted to determine the effect of the distribution of missing viral load test results for patients in care (and eligible for testing) by first considering all missing test results as unsuppressed and second as suppressed.[29] An on-treatment analysis was also performed, including only patients in the denominator who had an available viral load result for each particular 6-monthly interval. (All available viral load results for a particular patient were used for both the ITT and on-treatment analyses.)

As an additional sensitivity analysis, multivariable models of all outcomes were run restricted to patients enrolled at PHC clinics. Analyses were performed with Stata version 11.1 (College Station, TX). The study was approved by the University of Cape Town Research Ethics Committee.

RESULTS

Database records for 136,524 patients were reviewed for inclusion in analyses. Patients excluded were 5271 from 4 sites that did not collect baseline demographic or outcome data; 22,096 patients who were transferred-in to sites already receiving ART; 6686 who were younger than 16 years of age; 15,525 from sites at which no patients received CBAS; 15,421 who started ART during the 6 months before site database closure, 2537 who had zero observation time, and 2035 patients with unknown group allocation at the start of ART. A total of 66,953 of 136,524 (49%) patients from 57 sites were thus included; of whom, 19,668 (29.4%) received CBAS and 47,285 (70.6%) did not.

Table 1 shows patients' baseline characteristics. CBAS patients had more advanced WHO clinical stage disease, more concurrent TB, a slightly higher baseline CD4 cell count, were enrolled on ART during the more recent study period, and were more likely to be enrolled at PHC facilities. Compared to the Western Cape, CBAS patients were approximately 2-fold more likely to be enrolled in the Eastern Cape and Mpumalanga, provinces in which higher ART patient

TABLE 1. Characteristics of Patients at the Start of ART Receiving and Not Receiving Community-Based Adherence Support

Characteristics	Patients Received CBAS (n = 19,668)	Patients Without CBAS (n = 47,285)	RR (95% CI)
Median age, yrs (IQR), n = 66,953	35.1 (29.4–42.3)	34.6 (29.3–41.4)	
Male gender, n (%), n = 66,953	5955 (30.3%)	15,154 (32.1%)	0.94 (0.92 to 0.97)
WHO clinical stage, n (%),* n = 45,785			
I/II	3268 (26%)	9810 (29.5%)	0.89 (0.86 to 0.92)
III	7874 (62.7%)	20,250 (60.9%)	Reference
IV	1412 (11.3%)	3173 (9.6%)	1.10 (1.05 to 1.15)
CD4 cell count, median (IQR) (cells/μL), (n = 56,206)	132 (73–181)	122 (63–173)	
CD4 cell categories, n (%)*			
<100	5902 (36.3%)	16,351 (40.9%)	0.91 (0.88 to 0.94)
101–200	7952 (48.9)	19,312 (48.3%)	Reference
>200	2394 (14.7%)	4295 (10.8%)	1.23 (1.18 to 1.27)
TB treatment, n (%),* n = 60,158	2762 (14.3%)	5170 (12.6%)	1.10 (1.07 to 1.14)
Pregnancy, n (%),* n = 62,412	928 (4.8%)	1713 (4%)	1.14 (1.08 to 1.20)
Initial ART regimen, n (%),* n = 57,338			
d4T-3TC-EFV	11,437 (62.6%)	25,828 (66.1%)	Reference
d4T-3TC-NVP	3686 (20.2%)	9540 (24.4%)	0.91 (0.88 to 0.94)
ZDV-3TC-EFV	295 (1.6%)	371 (1%)	1.44 (1.32 to 1.57)
ZDV-3TC-NVP	322 (1.8%)	245 (0.6%)	1.84 (1.71 to 1.99)
TDF-3TC-EFV	1857 (10.2%)	2061 (5.3%)	1.54 (1.48 to 1.60)
TDF-3TC-NVP	660 (3.6%)	1036 (2.7%)	1.27 (1.19 to 1.35)
Year of starting ART, median (IQR), n = 66,953	2009 (2008–2010)	2008 (2007–2010)	
Categories of year of starting ART, n (%)			
2004–2006	2123 (10.8%)	7310 (15.5%)	Reference
2007–2008	5763 (29.3%)	18,981 (40.1%)	1.03 (0.99 to 1.08)
2009–2010	11,782 (59.9%)	20,994 (44.4%)	1.59 (1.53 to 1.66)
PHC-based care, n (%), n = 66,953	17,198 (87.4%)	30,796 (65.1%)	2.75 (2.64 to 2.86)
Rural ART facility, n (%), n = 66,953	996 (5.1%)	3089 (6.5%)	0.82 (0.78 to 0.87)
Province, n (%), n = 66,953			
Western Cape	2381 (12.1%)	6273 (13.3%)	Reference
Eastern Cape	6013 (30.6%)	5874 (12.4%)	1.84 (1.78 to 1.91)
Kwazulu-Natal	7670 (39%)	32,741 (69.2%)	0.69 (0.66 to 0.72)
Mpumalanga	3604 (18.3%)	2397 (5.1%)	2.18 (2.10 to 2.27)

*Proportions of available values.
3TC = lamivudine; d4T = stavudine; EFV = efavirenz; NVP = nevirapine; TDF = tenofovir; ZDV = zidovudine.

mortality is reported[31] and which reflects the relative distribution of adherence support across the network of sites.

The total observation time was 100,295 person-years with a median follow-up duration of 14.8 months [interquartile range (IQR): 7.7–25.5], being equivalent between patients with and without CBAS ($P = 0.39$). During the study period, 970 (4.9%) CBAS patients and 2968 (6.3%) non-CBAS patients died. A total of 1185 (6%) CBAS patients and 4498 (9.5%) non-CBAS patients became LTFU.

After 5 years of treatment, the Kaplan–Meier estimates of patient retention were 79.1% (95% CI: 77.7% to 80.4%) in CBAS patients versus 73.6% (95% CI: 72.6% to 74.5%) in non-CBAS patients; crude hazard ratio (HR) for attrition was 0.68 (95% CI: 0.65 to 0.72; $P < 0.0001$). After 5 years, LTFU was 13.2% (95% CI: 12% to 14.4%) in CBAS patients versus 17.7% (95% CI: 16.8% to 18.6%) in non-CBAS patients; crude HR was 0.62 (95% CI: 0.59 to 0.67; $P < 0.0001$); and mortality was 9% (95% CI: 8% to 10%) in CBAS patients versus 10.6% (95% CI: 10% to 11.3%) in non-CBAS patients; crude HR was 0.77 (95% CI: 0.72 to 0.83; $P < 0.0001$) (Fig. 1). During the first 3 months of treatment, the rate of attrition in CBAS patients was 15.1 persons/100 person-years (95% CI: 14.1 to 16.3) versus 25 persons/100 person-years (95% CI: 24.1 to 26) in non-CBAS patients, incidence rate ratio 0.61 (95% CI: 0.56 to 0.66).

In multivariable analyses using the imputed data sets (Table 2), patients who received CBAS had independently reduced mortality after starting ART, adjusted HR (aHR) was 0.65 (95% CI: 0.59 to 0.72). The NNT to prevent one death at 1 and 3 years were 10.2 (95% CI: 7.8 to 14.2) and 8.4 (95% CI: 6.6 to 11.6), respectively. Low baseline CD4 cell count was strongly predictive of mortality, and mortality was increased by 2- to 3-fold in Mpumalanga and Eastern Cape provinces compared with the Western Cape. The proportion

of imputed baseline covariate values were as follows: CD4 cell count, 16.1%; pregnancy status, 6.8%; TB treatment, 10.1%; WHO clinical stage, 31.6%; and initial regimen, 14.4%. In a sensitivity model using complete-subjects analysis, the adjusted effect measure for mortality in CBAS patients was similar (Table 2). When stratifying models of mortality by baseline CD4 cell count (complete subjects), the association of CBAS with reduced mortality was more pronounced among patients with baseline CD4 cell counts of 0–200 cells/μL [aHR: 0.59 (95% CI: 0.53 to 0.64)] than in patients with baseline CD4 cell counts greater than 200 cells/μL [aHR: 0.88 (95% CI: 0.64 to 1.23)].

LTFU was reduced in CBAS patients in multivariable analyses, aHR was 0.63 (95% CI: 0.59 to 0.68) (Table 2). The NNT to prevent one case of LTFU at 1 and 3 years were 8.3 (95% CI: 7 to 10.3) and 6.5 (95% CI: 5.7 to 8), respectively. The complete-subjects analysis aHR for LTFU was similar: 0.70 (95% CI: 0.64 to 0.76). The association of CBAS with reduced LTFU did not vary significantly in magnitude across categories of other covariates.

In total, 62,611 viral load results were available for analyses. Figure 2 shows proportions of patients achieving VS according to duration of ART. In ITT analyses (Fig. 2A), VS was 76.6% (95% CI: 75.8% to 77.5%) in CBAS patients versus 72% (95% CI: 71.3% to 72.5%) in non-CBAS patients after 6 months of ART ($P < 0.0001$). Table 3 indicates effect measures of VS at 6-monthly intervals after starting ART. VS was greater in patients who received CBAS and increased in magnitude for longer durations of ART: After 1 and 5 years of ART, the adjusted estimates were aOR: 1.33 (95% CI: 1.24 to 1.43) and aOR: 2.66 (95% CI: 1.61 to 4.40), respectively. In a summary model of VS over 5 years, adjusted for all measured baseline characteristics and duration of ART, the aOR associated with CBAS was 1.49 (95% CI: 1.40 to 1.58). Patients with lower baseline CD4 cell counts had a progressively decreased probability of achieving VS [<50 cells/μL, aOR: 0.50 (CI: 0.45 to 0.56); 50–100 cells/μL, aOR: 0.68 (CI: 0.61 to 0.76) compared with >200 cells/μL].

Overall, 52.1% and 50.9% of viral load results were unavailable for patients in care (eligible for testing) among CBAS and non-CBAS patients, respectively [RR: 1.02 (95% CI: 1.02 to 1.03)]. As illustrated in Figures 2B, C, improved virological suppression in CBAS patients remained evident in sensitivity analyses when considering all missing test results either as suppressed [aOR: 1.44 (95% CI: 1.37 to 1.52)] or as unsuppressed [aOR: 1.15 (95% CI: 1.11 to 1.19)]. In on-treatment analyses, virologic suppression was equivalent (months 36–60) to marginally poorer (months 6–30) in patients receiving CBAS; overall RR 0.97 was (95% CI: 0.96 to 0.97) (Fig. 2D).

Median increases in CD4 cells after 1 and 3 years of ART were 159 cells/μL (IQR: 81–253; n = 10,955) and 277 cells/μL (IQR: 157–423; n = 2267), respectively, and were equivalent between groups ($P = 0.56$ and $P = 0.51$, respectively).

When restricting analyses to patients enrolled at PHC clinics, adjusted effect measures for CBAS versus non-CBAS patients were similar to those for the full cohort: mortality aHR was 0.64 (95% CI: 0.58 to 0.70); LTFU aHR was 0.63 (95% CI: 0.58 to 0.68); and virological suppression (ITT summary model over 5 years) aOR was 1.44 (95% CI: 1.35 to 1.54).

DISCUSSION

This study provides data on the effectiveness of the large-scale implementation of CBAS programs in 4 South African provinces with up to 5 years of patient follow-up. Patients receiving CBAS had a 35% reduction in mortality and a 37% reduction in LTFU when compared with those without.

Virological suppression was also superior in CBAS patients, the magnitude of which increased for longer durations of therapy. Patients on long-term ART are at risk of "treatment fatigue" (ie, patients tiring after taking ART over long periods of time),[1,19] which may be mitigated by community adherence support. In Uganda, greater improvement in virologic outcomes was also described with increasing durations of treatment among patients supported by peer health workers compared with controlls.[19]

The reduction in LTFU associated with CBAS did not vary across categories of baseline CD4 cell count. Mortality, in contrast, was reduced to a greater extent in CBAS patients

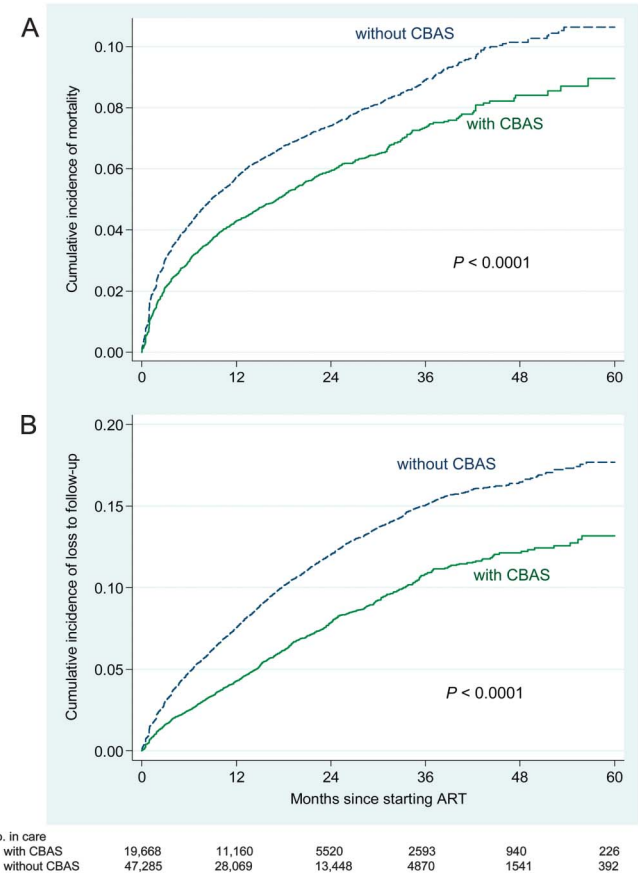

FIGURE 1. Cumulative incidences of (A) mortality and (B) LTFU after starting ART in patients who received and did not receive community-based adherence support.

TABLE 2. Crude and Adjusted HRs of Mortality and LTFU After Starting Antiretroviral Treatment

	Mortality			LTFU		
		Adjusted HR (95% CI)			Adjusted HR (95% CI)	
Predictor of Mortality or LTFU	Crude HR (95% CI)	Multiple Imputation*	Complete Subjects†	Crude HR (95% CI)	Multiple Imputation*	Complete Subjects†
Patients received CBAS						
Yes	0.77 (0.72 to 0.83)	0.65 (0.59 to 0.72)	0.63 (0.56 to 0.70)	0.62 (0.59 to 0.67)	0.63 (0.59 to 0.68)	0.70 (0.64 to 0.76)
No	Reference	Reference	Reference	Reference	Reference	Reference
Gender						
Male	1.60 (1.51 to 1.71)	1.38 (1.30 to 1.48)	1.38 (1.26 to 1.50)	1.23 (1.16 to 1.30)	1.30 (1.23 to 1.38)	1.34 (1.24 to 1.44)
Female	Reference	Reference	Reference	Reference	Reference	Reference
Age (continuous), yrs	1.01 (1.01 to 1.02)	1.01 (1.01 to 1.01)	1.01 (1.01 to 1.02)	0.98 (0.98 to 0.98)	0.98 (0.98 to 0.98)	0.98 (0.97 to 0.98)
Baseline CD4 cell count category, cells/μL						
<50	3.89 (3.31 to 4.56)	3.28 (2.78 to 3.86)	3.17 (2.58 to 3.89)	1.48 (1.31 to 1.66)	1.36 (1.20 to 1.53)	1.34 (1.16 to 1.55)
50–100	2.29 (1.93 to 2.70)	2.04 (1.71 to 2.43)	1.90 (1.53 to 2.35)	1.22 (1.08 to 1.38)	1.21 (1.06 to 1.37)	1.19 (1.02 to 1.37)
101–200	1.23 (1.05 to 1.45)	1.18 (1.00 to 1.40)	1.15 (0.94 to 1.42)	1.03 (0.92 to 1.15)	1.06 (0.94 to 1.19)	1.03 (0.90 to 1.18)
201–350	Reference	Reference	Reference	Reference	Reference	Reference
>350	0.80 (0.54 to 1.18)	0.69 (0.47 to 1.01)	0.45 (0.25 to 0.80)	1.07 (0.85 to 1.34)	0.98 (0.77 to 1.23)	0.62 (0.43 to 0.88)
Baseline WHO clinical stage						
I–II	Reference	Reference	Reference	Reference	Reference	Reference
III–IV	1.92 (1.74 to 2.13)	1.58 (1.41 to 1.75)	1.42 (1.27 to 1.60)	1.20 (1.11 to 1.28)	1.14 (1.06 to 1.23)	1.13 (1.03 to 1.22)
Baseline TB treatment	1.12 (1.02 to 1.23)	0.97 (0.86 to 1.10)	0.98 (0.88 to 1.12)	0.98 (0.90 to 1.07)	1.06 (0.96 to 1.17)	1.07 (0.97 to 1.19)
Pregnancy status						
Pregnant women	0.35 (0.26 to 0.47)	0.52 (0.39 to 0.70)	0.50 (0.34 to 0.74)	1.35 (1.19 to 1.53)	1.30 (1.13 to 1.49)	1.42 (1.21 to 1.67)
Nonpregnant women	Reference	Reference	Reference	Reference	Reference	Reference
Year of starting ART (per annual increase)	0.85 (0.83 to 0.87)	0.82 (0.80 to 0.84)	0.76 (0.74 to 0.79)	1.01 (0.99 to 1.03)	1.08 (1.06 to 1.10)	1.07 (1.04 to 1.10)
Initial regimen NRTI						
ZDV	0.83 (0.63 to 1.10)	1.22 (0.84 to 1.78)	1.13 (0.74 to 1.73)	0.99 (0.80 to 1.23)	1.02 (0.82 to 1.27)	1.18 (0.88 to 1.60)
d4T	Reference	Reference	Reference	Reference	Reference	Reference
TDF	0.49 (0.41 to 0.59)	0.82 (0.64 to 1.04)	0.87 (0.67 to 1.13)	0.49 (0.42 to 0.58)	0.58 (0.49 to 0.70)	0.61 (0.49 to 0.77)
Initial regimen NNRTI						
EFV	Reference	Reference	Reference	Reference	Reference	Reference
NVP	0.58 (0.53 to 0.63)	0.94 (0.83 to 1.06)	0.95 (0.84 to 1.07)	1.01 (0.95 to 1.08)	0.98 (0.92 to 1.05)	1.02 (0.94 to 1.12)
Level of care						
PHC clinics	0.85 (0.79 to 0.91)	1.00 (0.92 to 1.08)	1.06 (0.96 to 1.17)	0.78 (0.74 to 0.82)	0.86 (0.80 to 0.92)	0.92 (0.84 to 1.00)
Hospitals	Reference	Reference	Reference	Reference	Reference	Reference
Rural/urban site						
Rural	1.83 (1.65 to 2.03)	2.07 (1.84 to 2.31)	1.56 (1.28 to 1.89)	0.78 (0.74 to 0.82)	0.62 (0.53 to 0.71)	0.49 (0.39 to 0.63)
Urban	Reference	Reference	Reference	Reference	Reference	Reference
Province						
Western Cape	Reference	Reference	Reference	Reference	Reference	Reference
KwaZulu-Natal	1.31 (1.17 to 1.46)	1.41 (1.25 to 1.59)	1.42 (1.20 to 1.67)	1 (0.93 to 1.08)	1 (0.92 to 1.09)	0.95 (0.85 to 1.07)
Eastern Cape	1.78 (1.58 to 2.01)	2.78 (2.42 to 3.19)	3 (2.47 to 3.62)	1.04 (0.95 to 1.15)	1.27 (1.14 to 1.41)	1.24 (1.07 to 1.44)
Mpumalanga	1.37 (1.18 to 1.60)	2.24 (1.89 to 2.65)	1.69 (1.27 to 2.24)	0.71 (0.62 to 0.81)	0.99 (0.86 to 1.14)	0.59 (0.46 to 0.76)

HRs are from Cox proportional hazards regression models. Crude models analyzed each variable by itself. Adjusted models were adjusted for all variables appearing in the table.
*Multivariable models derived from multiple imputation of missing covariate values by chained equations using 10 imputed data sets (n = 66,953).
†Multivariable models derived using complete-subjects analysis (n = 36,344).
d4T = stavudine; EFV = efavirenz; NVP = nevirapine; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; TDF = tenofovir; ZDV = zidovudine.

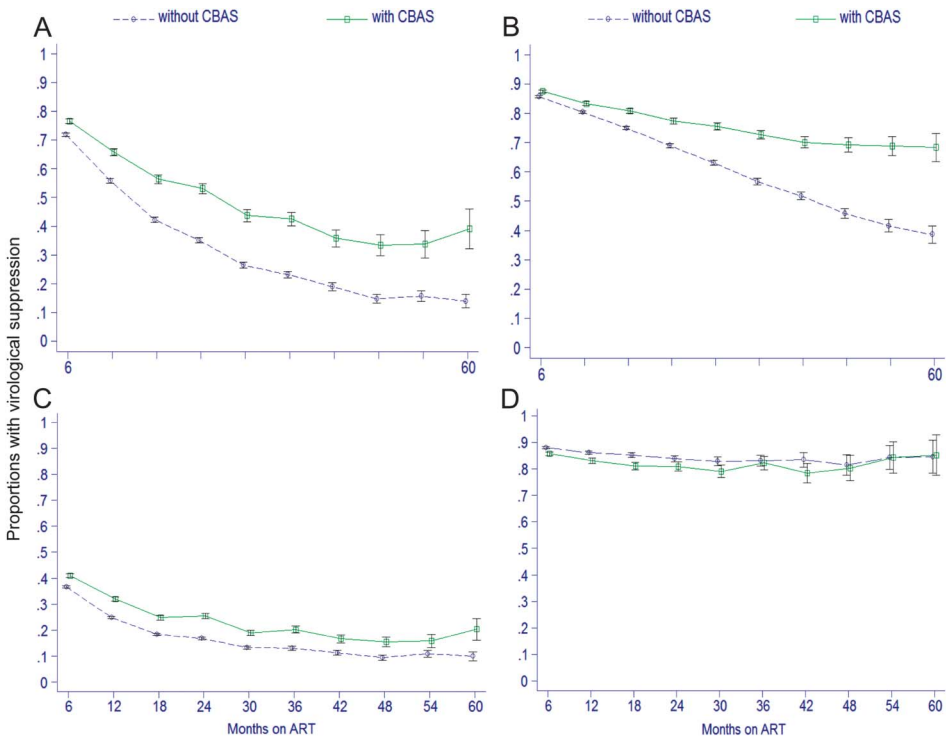

FIGURE 2. Proportions of patients achieving virological suppression in (A) ITT analyses censoring missing values, (B) ITT analyses regarding missing values as suppressed, (C) ITT analyses regarding missing values as unsuppressed and (D) on-treatment analyses. Error bars are 95% CIs.

with lower baseline CD4 cell counts (<200 cells/μL). Low baseline CD4 cell count itself was strongly predictive of both mortality and reduced virologic suppression, as demonstrated in previous studies.[5,32,33] Patients with low baseline CD4 cell counts in the CBAS group in whom mortality may have been averted through improved adherence would, nevertheless, remain at increased risk of having a subsequently unsuppressed viral load, that is, CBAS would retain a larger pool of patients at increased risk of having unsuppressed viral loads. This may be the reason that no improvement in virological suppression was seen among CBAS patients in on-treatment analyses. The ITT approach is, however, a preferable analytic method for the pragmatic assessment of the effect of an intervention[29,34] and demonstrated improved virologic suppression in CBAS patients. LTFU was higher in the non-CBAS group, and patients who are truly LTFU would have unsuppressed viral loads.[35]

Improved outcomes in patients receiving CBAS are likely due to overcoming of denial, improved knowledge of HIV/AIDS, understanding the importance of adherence, and

TABLE 3. Virological Suppression in Patients Who Received and Did Not Receive Community-Based Adherence Support at 6-Monthly Intervals on ART*

Months of ART	Patients Received CBAS n suppressed/N (%)	Patients Without CBAS n suppressed/N (%)	Crude RR (95% CI)	aOR† (95% CI)
6	7266/9481 (76.6)	15,458/21,478 (72)	1.06 (1.05 to 1.08)	1.22 (1.14 to 1.30)
12	4004/6087 (65.8)	8,271/14,813 (55.8)	1.18 (1.15 to 1.21)	1.33 (1.24 to 1.43)
18	2291/4068 (56.3)	4725/11,183 (42.3)	1.33 (1.29 to 1.38)	1.46 (1.34 to 1.59)
24	1724/3248 (53.1)	3143/8954 (35.1)	1.51 (1.45 to 1.58)	1.57 (1.42 to 1.72)
30	918/2100 (43.7)	1719/6507 (26.4)	1.65 (1.55 to 1.76)	1.80 (1.58 to 2.06)
36	714/1681 (42.5)	1088/4709 (23.1)	1.84 (1.70 to 1.98)	2.20 (1.87 to 2.59)
42	378/1057 (35.8)	600/3169 (18.9)	1.89 (1.70 to 2.10)	2.27 (1.79 to 2.88)
48	216/649 (33.4)	317/2157 (14.7)	2.26 (1.95 to 2.62)	2.50 (1.79 to 3.49)
54	124/371 (33.7)	220/1405 (15.7)	2.13 (1.77 to 2.57)	2.61 (1.72 to 3.98)
60	75/192 (39.1)	110/791 (13.9)	2.80 (2.19 to 3.60)	2.66 (1.61 to 4.40)

*Analyses were by ITT (denominator includes all patients allocated to each group with follow-up till each respective time interval, excluding patients with missing values).

†Odds ratios were derived from logistic regression of CBAS versus non-CBAS patients adjusting for age, gender, baseline CD4 cell count, baseline WHO clinical stage, initial regimen, baseline pregnancy, TB status, rural/urban nature of site, province, and level of care. Models used imputed data for missing covariate values and were adjusted for clustering by site.

OR = odds ratio.

improvement in psychosocial problems which in turn lead to improved behavior skills related to adherence.[36] CBAS also likely reduces stigmatization due to HIV/AIDS and leads to greater social capital (community relationships).[37] CBAS is expected to widen the "community safety net"[38] and heighten social responsibility, with positive effects on adherence and clinic attendance, as adherence to ART in Africa is not merely an individual activity but a community effort.[39]

In addition to adherence support and health education, PAs assist with access to social pensions and grants. This is expected to improve the households' economic status and reduce food insecurity, which can improve survival.[40]

The company cost per PA (including support services costs in January 2012) is USD 225–275 per PA per month, with an approximate cost of USD 1.88–3.43 per patient per month and an approximate cost of USD 1.98 per patient visit (average of 6 patients visited per day per PA). Low-cost interventions that reduce LFTU substantially improve both program effectiveness and cost-effectiveness in low-income settings.[41] The PA program is a low-cost intervention, which can be introduced in low-income settings. In addition, this intervention is a source of job creation and provides a potential for further career development for PAs.[42]

The strengths of this study include the large sample size from a number of different sites, which has allowed precise estimation of effect measures. Prospective individual-level data were collected enabling controlling for patient factors associated with outcomes. Effect measures from multivariable analyses using imputed data sets, complete-subjects methods, and sensitivity analyses showed the same direction of effect and were of similar magnitude. Missing viral load results and the lack of effect seen in on-treatment virological analyses does, nevertheless, reduce the strength of the conclusion of improved virological suppression due to CBAS.

Other limitations relate to the use of routine data and the nonrandomized allocation of patients to groups, with the potential for information bias and unmeasured confounding. However, the prestudy probability of these findings was high, as the results concur with previous smaller studies.[43] As CBAS workers were more active in geographic areas closer to local clinics, non-CBAS patients may have lived at greater distances from ART facilities. Living further from the clinic may slightly increase the risk of LTFU and may have been an unmeasured confounder in the relationship between CBAS and LTFU. However, similar to our results, LTFU was substantially reduced in CBAS patients in a randomized trial in Uganda,[19] suggesting that CBAS truly reduces LTFU. Baseline socioeconomic factors may be associated with mortality and were potential unmeasured confounders. However, previous South African analyses showed that CBAS patients were not more socioeconomically advantaged than non-CBAS patients,[17] thus socioeconomic differences are unlikely to have confounded effect measures in favor of CBAS. Although measured baseline characteristics between the groups were dissimilar, the large data set may produce statistically significant baseline differences between groups that may not necessarily be clinically meaningful. In addition, residual confounding is unlikely to have confounded effect measures in favor of CBAS as most potential confounders associated with poor outcome were more prevalent in CBAS patients (advanced clinical stage,[44] concurrent TB,[45] more recent year of starting ART,[4,5] and provincial distribution). Missing viral load results may bias virologic outcomes; however, effect measures from extreme-case sensitivity analyses pointed in the same direction as the primary analyses. Missing data values from routine ART programs in sub-Saharan Africa are common.[4,46,47] Reasons for this include a lack of data capturers, overwhelmed administrative systems, a low return of laboratory results, poor clerical support at clinical sites leaving results unfiled, and inadequate training of clinical staff regarding data collection. Attempts are underway to improve data completeness through improving clinical and data staff training and improving systems for capturing relevant data and laboratory results. In addition, the South African government is rolling out Tier.net, a national system for data collection for ART patients.

All sites were supported by an NGO, and it is possible that outcomes may not be well generalizable to non–NGO-supported government health facilities; however, the large number of sites included raises the likelihood that subjects were well representative of South African public sector ART patients. It is possible that patients who declined consent for PA support had increased psychosocial issues (such as denial) that may have been adversely associated with retention. Due to the large size of the cohort, patients LTFU were not tracked and linkage with the national death registry was not performed. Adherence determination data were not analyzed, as there are no standard government protocols or tools to measure patient-level adherence.

In conclusion, the large-scale implementation of low-cost CBAS programs is shown to improve survival, retention in care and virological outcomes for adults receiving ART, with benefit sustained or increasing up to 5 years after starting ART. Further scale-up of these programs should be considered for the increasing number of patients receiving ART in low-income settings where the professional health care workforce is limited.

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