

Geoffrey Fatti MBChB MPH, Ashraf Grimwood MBChB MPH, and Peter Bock MBChB MRCP MRCGP MPH

Khethimpilo, Cape Town, South Africa



## Introduction

There have been conflicting results of the effectiveness of antiretroviral therapy (ART) provision between primary healthcare (PHC) facilities and hospitals in low-income settings. Outcomes at PHC facilities were superior within a subdistrict in Lusikisiki, South Africa,<sup>1</sup> however a recent Malawian study reported increased mortality amongst ART patients attending PHC facilities.<sup>2</sup> This comparison has not been evaluated on a broad scale in South Africa. We compared baseline characteristics and treatment outcomes between patients managed at different levels in the health system and quantified baseline determinants of poor longitudinal outcome in a cohort from four provinces in South Africa, representing over 7% of South African public-sector ART patients enrolled between 2004 and 2007.

## Method

A retrospective cohort study was performed using routine electronic data of ART-naïve adults from 47 PHC facilities, nine district hospitals and three regional hospitals, where an externally-funded nongovernmental organisation (NGO) named Absolute Return for Kids South Africa (subsequently called Kheth'Impilo) assisted the DOH in the rollout of the ART program. Outcome measures were death, loss to follow-up (LTFU), virological suppression (VS) and CD4 cell count increases. LTFU was defined as no visit to the clinic for three months or more beyond

the last missed appointment date and virologic suppression (VS) as a viral load < 400 copies/ml. Prospective individual-level patient data was collected for routine monitoring purposes by designated site-based data captureurs at each patient visit. Kaplan-Meier estimates, multi-variable competing-risks Cox regression, logistic regression and generalised estimating equation population-averaged models were used to compare outcomes between levels of care adjusting for baseline clinical and demographic variables.

## Results

29,203 adults (68.1% women) having 29,297 person-years of observation were included in the analysis. Sixty-six percent, 8.5% and 25.5% of patients enrolled at PHC facilities, district hospitals and regional hospitals respectively, **table 1**. The mean number of patients enrolled per facility at regional hospitals was 2482

	Primary healthcare	District Hospitals	Regional Hospitals	P-value
Number of patients, n (%)	19 273 (66.0)	2483 (8.5)	7447 (25.5)	
Number of sites	47	9	3	
Mean patients enrolled/site	410	311	2482	
Median age, y (IQR)	34.0 (29.2–40.4)	34.7 (29.9–41.6)	34.8 (29.7–41.5)	0.001
Male, % (95% CI)	32.0 (31.3–32.6)	31.4 (29.6–33.2)	31.9 (30.8–33.0)	0.827
WHO stage ≥III, % (95% CI)	79.3 (78.6–79.9)	58.3 (55.9–60.8)	72.2 (71.0–73.3)	<0.001
CD4 count, median (IQR)	113 (57–165)	109 (54–155)	116 (57–170)	0.001

compared to 410 at PHC sites. Baseline CD4 cell counts were similar between facility levels (overall median 114

cells/μL (IQR: 57–166), however patients enrolling at PHC sites had more severe clinical stage disease (P < 0.001).

During the study period, 1076 (5.6%), 182 (7.3%) and 398 (5.3%) patients died at PHC facilities, district and regional hospitals respectively (P = 0.001), and 1719 (8.9%), 348 (14.0%) and 1334 (17.9%) patients become LTFU at PHC facilities, district and regional hospitals respectively (P < 0.001). **Figure 1** shows Kaplan-Meier cumulative estimates of RIC, mortality, LTFU and transfer-out between levels of care. RIC was superior at PHC facilities, being 76.3% (95% CI: 74.6%–77.8%) compared to 67.5% (95% CI: 63.8%–70.8%) and 66.5% (95% CI: 65.0%–68.0%) at district and regional hospitals respectively after 36 months of ART (logrank P < 0.0001). Mortality was highest at district hospitals, being 10.3% (95% CI: 8.9%–12.0%) compared to 6.9% (95% CI: 6.2%–7.7%) and 8.0% (95% CI: 7.4%–8.8%) at regional hospitals and PHC facilities respectively after 36 months, logrank P < 0.0001. LTFU was significantly higher at district and regional hospitals (P < 0.0001) Transfer out increased dramatically after 24 months at regional hospitals.

In adjusted regression analyses of baseline factors associated with death and LTFU after 12 months of ART (n = 18 866), LTFU was independently increased at regional hospitals (aHR 2.19; 95% CI: 1.94–2.47) and mortality was independently elevated at district hospitals (aHR 1.60; 95% CI: 1.30–1.99) compared to PHC sites, **table 2**. In addition, men had a slight independently increased risk of death and LTFU. Older age was inversely related to the risk of LTFU. Patients enrolling in

Table 2: Multivariable competing-risks Cox proportional hazards model of factors associated with death and loss to follow-up after 12 months of ART (n=18 866).

Patient Factor	Death		Loss to follow-up	
	Adjusted Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
Male gender	1.14	1.00–1.30	1.20	1.09–1.33
Age <sup>a</sup>	1.06	0.99–1.15	0.89	0.84–0.94
WHO stage I/II <sup>b</sup>	1			
stage III	1.85	1.47–2.32	1.15	1.01–1.32
stage IV	4.84	3.72–6.31	1.97	1.67–2.34
Baseline CD4 cell count (cells/μL)				
>200 <sup>b</sup>	1		1	
50–199	1.61	1.09–2.38	1.31	1.07–1.62
25–49	3.07	2.00–4.75	1.51	1.18–1.92
<25	3.80	2.48–5.82	1.49	1.17–1.89
Facility level				
Primary healthcare <sup>b</sup>	1		1	
District hospitals	1.60	1.30–1.99	1.36	1.11–1.66
Regional hospitals	1.07	0.91–1.27	2.19	1.94–2.47
Year of starting ART				
2004 <sup>b</sup>	1		1	
2005	0.87	0.67–1.14	3.05	2.09–4.44
2006	0.69	0.53–0.90	6.78	4.59–9.72
2007	0.49	0.37–0.65	6.18	4.30–8.89

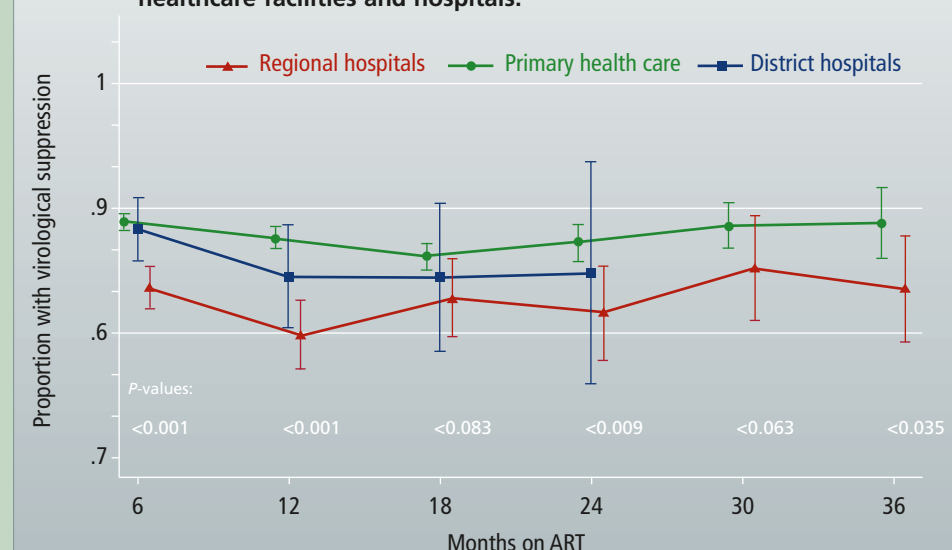
<sup>a</sup> 10-year age increase <sup>b</sup> Reference category

later years had considerably elevated risks of LTFU compared to patients enrolled in 2004.

The median CD4 cell increase after twelve months of treatment was 159 cells/μL (IQR: 81–254), with no difference between PHC sites and hos-

pitals (P = 0.44). Overall VS was highest at PHC facilities, being 88.0% (95% CI: 87.6%–88.4%) compared to 86.9% (95% CI: 84.8%–88.8%) and 82.2% (95% CI: 81.0%–83.4%) at district and regional hospitals respectively at any time-point on treatment, P < 0.001. **Figure 2** indicates virological suppression between facility levels. Using a multivariable model predicting virological suppression up to 36 months of ART adjusting for all available baseline variables (n = 10 697), district and regional

Figure 2: Proportions of patients with virological suppression at primary healthcare facilities and hospitals.



hospitals patients had independently reduced probabilities of VS compared to PHC facility patients, aOR 0.71 (95% CI: 0.55–0.90) and 0.66 (95% CI: 0.58–0.75) respectively (**table 3**). Length of time on ART for follow-up durations of more than 6 months was inversely associated with VS until 24 months on ART, but this became non-significant between 30–36 months (P = 0.32). In sensitivity analyses of baseline factors associated with VS at 12 months adjusting for all available baseline measurements (n = 4885), district and regional hospitals patients similarly had reduced probabilities of VS compared to PHC facility patients, aOR 0.73 (95% CI: 0.49–1.09) and 0.58 (95% CI: 0.45–0.75) respectively.

Table 3: Multivariable generalized estimating equation population-averaged model of virological suppression up to 36 months of ART. (n = 10 697)<sup>a</sup>

Variable	Adjusted OR	95% CI	P-value
Male gender	0.92	0.82–1.03	0.137
WHO stage: I/II <sup>b</sup>	1.00		
III/IV	0.85	0.75–0.96	0.008
Baseline CD4 cell count (μL)	1.00	0.99–1.00	0.780
Primary healthcare facilities <sup>b</sup>	1.00		
District hospitals	0.71	0.55–0.90	0.005
Regional hospitals	0.66	0.58–0.75	<0.001

<sup>a</sup> adjusted for year of starting ART and age <sup>b</sup> reference category

## Discussion

Patients treated at PHC facilities had superior longitudinal outcomes, despite having more advanced clinical stage disease when starting ART. Facility-level factors that may negatively impact patient outcomes at hospital-based outpatient services include high patient loads and high patient/staff ratios at hospital-based outpatient services, leading to reduced individual patient attention from nurses and counsellors and a resultant decreased quality of care, increased LTFU and treatment failure. Environmental factors that may affect outcomes between levels of care include the distance, difficulty and cost of transport to health facilities. Access to care at the primary level is however easier and cheaper for patients,<sup>3</sup> with services being more aligned to ongoing patient needs and a decreased time to treatment initiation. These results support the recent Presidential mandate which has pledged an acceleration of the number of ART sites at the PHC level to attempt to overcome the treatment backlog. Paediatric care has also been shown to be as effective at the PHC level compared to hospital-based care.<sup>4</sup>

Non HIV-related co-morbidities and HIV-related diagnoses were not part of the routine monitoring data used in this study. Patients with co-morbidities may be more likely to initiate ART at hospital level and also to have poorer outcomes, therefore these are potential confounders that were not accounted for in the analysis and would negatively affect overall outcome estimates at hospital level compared to PHC sites. Differences may therefore be partially attributable to these confounders, the magnitude of which is indeterminate in this study (although probably not large as a relatively lesser proportion of patients are likely to have serious non HIV-related morbidity or HIV-related morbidity not reflected in baseline immunological status or WHO clinical staging).

## Conclusions

ART outcomes on a broad scale are superior at PHC facilities, suggesting ART should be increasingly devolved to this level across the country. Prospective research should be undertaken to determine the degree to which outcome differences between facility levels are attributable to facility level characteristics, environmental factors or due to patient clinical co-morbidity at hospital levels.

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