

Treatment outcomes of HIV-positive patients on first-line antiretroviral therapy in private versus public HIV clinics in Johannesburg, South Africa

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Background: Despite the widely documented success of antiretroviral therapy (ART), stakeholders continue to face the challenges of poor HIV treatment outcomes. While many studies have investigated patient-level causes of poor treatment outcomes, data on the effect of health systems on ART outcomes are scarce.

Objective: We compare treatment outcomes among patients receiving HIV care and treatment at a public and private HIV clinic in Johannesburg, South Africa.

Patients and methods: This was a retrospective cohort analysis of ART naïve adults (≥ 18.0 years), initiating ART at a public or private clinic in Johannesburg between July 01, 2007 and December 31, 2012. Cox proportional-hazards regression was used to identify baseline predictors of mortality and loss to follow-up (>3 months late for the last scheduled visit). Generalized estimating equations were used to determine predictors of failure to suppress viral load (≥ 400 copies/mL) while the Wilcoxon rank-sum test was used to compare the median absolute change in CD4 count from baseline to 12 months post-ART initiation.

Results: 12,865 patients initiated ART at the public clinic compared to 610 at the private clinic. The patients were similar in terms of sex and age at initiation. Compared to public clinic patients, private clinic patients initiated ART at higher median CD4 counts (159 vs 113 cells/mm³) and World Health Organization stage I/II (76.1% vs 58.5%). Adjusted hazard models showed that compared to public clinic patients, private clinic patients were less likely to die (adjusted hazard ratio [aHR] 0.50; 95% confidence interval [CI] 0.35–0.70) but were at increased risk of loss to follow-up (aHR 1.80; 95% CI 1.59–2.03). By 12 months post-ART initiation, private clinic patients were less likely to have a detectable viral load (adjusted relative risk 0.65; 95% CI 0.49–0.88) and recorded higher median CD4 change from baseline (184 cells/mm³ interquartile range 101–300 vs 158 cells/mm³ interquartile range 91–244), when compared to public clinic patients.

Conclusion: We identified differences in treatment outcomes between the two HIV clinics. Findings suggest that the type of clinic at which ART patients initiate and receive treatment can have an impact on treatment outcomes. Further research is necessary to provide more conclusive results.

Keywords: health systems, attrition, HIV programs, viral suppression

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Introduction

Adherence to treatment and patient retention in care are key to achieving good treatment outcomes in HIV care and management.^{1,2} In South Africa, HIV care is provided by both the public and private sector. Like in most developing countries, the private sector has a long history of antiretroviral therapy (ART) provision through donor-funded projects. Over the years, the public sector has become the major

provider of HIV care, resulting in the country having the largest free ART program globally.³ The provision of ART in the public sector is prescribed by the South African Department of Health (DoH) National ART treatment guidelines adapted from the World Health Organization (WHO). Health care providers in the private sector can use the South African DoH National ART treatment guidelines but it is not mandatory (Table 1). Initiation criteria and treatment are generally the same; however, the private sector has access to different drugs which are usually more expensive.⁴

Given the foregoing, there are challenges to the attainment of desired treatment outcomes, some unique to either sector. Health system factors include: clinical mismanagement, poor quality of HIV care, lack of standardization, and poor regulation of services.^{3,4} There are concerns of poor monitoring of HIV care and desired treatment outcomes in both sectors, particularly in the private sector where practitioners are often unregulated.³ These factors have a negative impact on treatment, leading to poorer treatment outcomes like mortality, and increased the risk of loss to follow-up (LTF). Attrition is more common in private clinics.^{4,5} The high costs of HIV drugs in this sector are identified as one of the driving factors of poor adherence to treatment and subsequent LTF. This suggests that patients in private clinics have a higher risk of developing viral resistance due to treatment interruptions than those in public clinics.⁵ The public sector

has its fair share of challenges. The overwhelming work load compromises the quality of HIV care,^{6,7} for example, counseling sessions are reduced or not done at all⁵ and the quality of counseling has been identified as a risk factor for patient retention in ART care.⁶ Lengthy queues at the clinic may deter patients from accessing drugs. Stigmatization,⁶ also common in the public sector, often leads to nonadherence to treatment and high rates of LTF.⁵

Extensive studies have been done to assess HIV treatment outcomes in the public sector,^{8–10} however, data on the differences in treatment outcomes between the public and private health care setting is scarce. Therefore, this study aimed to describe patients seeking care at a private or public HIV clinic in Johannesburg. We described differences in mortality, LTF, and viral suppression during early ART initiation (<12 months) where differences were most likely to be observed. We compared treatment outcomes and identified baseline predictors of all-cause mortality, LTF, failure to suppress viral load (≥ 400 copies/mL), and CD4 count change at 12-month post-ART initiation.

Patients and methods

Study site and subjects

A retrospective cohort study design was used to analyze routinely collected data from a public sector and a private sector HIV clinic. The Themba Lethu Clinic (TLC), representative

Table 1 Comparative description of study sites

Characteristic	Private clinic	Themba Lethu Clinic
Demographics		
Clinic size	Single HIV clinician who sees on average 25 patients per day	Modest medical staff complement of approximately 6–8 doctors that see approximately 400–500 patients per day (50–60 patients per doctor per day)
Characteristics of the patients	Most patients are educated and gainfully employed (79% and 86%, respectively). All patients are on medical aid. Cash patients are usually foreign	53% of patients are unemployed although the majority have above primary-level education
HIV management		
ART initiation criteria	2004 WHO guidelines ¹² Eligibility: CD4 cell count $\leq 200/\text{mm}^3$, regardless of WHO stage or WHO stage IV irrespective of CD4 count First-line regimen: AZT-3TC/NVP 2010 WHO guidelines ¹³ Eligibility: patients initiated with a CD4 cell count ≤ 350 cells/ mm^3 or WHO stage III or IV, coinfecting with tuberculosis (TB) or hepatitis B virus (HBV) irrespective of CD4 cell count First-line regimen: AZT/3TC/EFV or TDF/3TC/EFV (or NVP in place of EFV)	2004 South African DoH National ART treatment guidelines ¹⁴ Eligibility: CD4 cell count next 200/ mm^3 , regardless of WHO stage or WHO stage IV irrespective of CD4 count First-line regimen: d4T/3TC/EFV or d4T/3TC/NVP 2010 South African DoH National ART treatment guidelines ¹⁵ prior to April of the same year Eligibility: CD4 cell count < 200 cells/ mm^3 irrespective of clinical stage or CD4 count ≤ 350 cells/ mm^3 in patients coinfecting with TB or pregnant women or WHO stage IV irrespective of CD4 count First-line regimen: TDF and 3TC or FTC with EFV or NVP
ART monitoring	Viral load, AST, ALT, and CD4 count tests are collected every 3–4 month visit	Viral load, AST, ALT, and CD4 count tests are collected at 4–7 months after initiation of a new regimen, thereafter biannual or as clinically indicated

Abbreviations: ART, antiretroviral therapy; DoH, Department of Health; 3TC, lamivudine; NVP, nevirapine; WHO, World Health Organization; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; TDF, tenofovir; FTC, emtricitabine; AST, aspartate transaminase; ALT, alanine transaminase.

of the public sector, is located in the city of Johannesburg, Gauteng Province in North Central South Africa. Gauteng Province has an estimated HIV prevalence of 15.2% and has the second largest number of patients on ART in South Africa. The clinic is located in an ambulatory care wing of the Helen Joseph Hospital, a large urban public sector teaching hospital. The TLC is one of the largest comprehensive care, management, and treatment (CCMT) sites in South Africa and provides both pre-ART and ART care.¹¹ Since 2004, TLC has enrolled approximately 36,487 HIV-positive patients into its HIV care and treatment program. Approximately, 400–500 patients are seen per day by a modest clinical staff for medical and/or ART visits. There are six to eight full-time doctors, nine nurses, three pharmacists, and a team of five administrative and eight data entry staff (Table 1). Current numbers are down on earlier numbers following down referral to clinics and general practitioners (GPs) in the area.

The private clinic is located in Brenthurst, Parktown, Johannesburg. The clinic provides private HIV care and treatment where patients pay for services and drugs either by cash or through medical-aid schemes. The clinic has been operational since 2007 and is managed by a single HIV clinician. By December 2012, the clinic had enrolled approximately 3,857 patients on ART. On average, 25 patients are seen per day at this clinic.

The study included ART naïve HIV-positive adults eligible for ART initiation according to either the WHO guidelines^{12,13} or the South African DoH National ART treatment guidelines^{14,15} and initiated on standard first-line ART between July 1, 2007 and December 1, 2012¹² (Table 1). Prior to April 2010, eligibility for ART required a CD4 count of ≤ 200 cells/mm³. This has since risen to ≤ 350 cells/mm³.³ The patients were given a first-line regimen recommended by the WHO consisting of two nucleoside reverse transcriptase inhibitors (stavudine, lamivudine, and tenofovir were introduced after 2010) and one non-nucleoside transcriptase inhibitor (efavirenz).^{3,12–16} However, stavudine was prescribed minimally at the private clinic.

We excluded patients who transferred into either clinic from other sites, minors (< 18.0 years of age), those who initiated ART outside the study period, treatment-experienced patients, and pregnant females. We excluded pregnant at ART initiation as pregnant women are typically placed on the boosted protease inhibitor Kaletra (lopinavir and ritonavir) while nonpregnant women with declared pregnancy intentions at baseline are placed on nevirapine rather than efavirenz.¹⁷ In addition, we excluded transfer-ins (patients who transferred on ART into either clinic) as these patients generally do not have a record of earlier ART or baseline clinical or laboratory information at ART initiation.

Data collection and management

Data are collected from each site's routinely maintained electronic medical records, which are entered and stored in an information system called TherapyEdge-HIV™ (Associated Biological Systems, Johannesburg, South Africa). For this study, paper-based medical records kept by the sites were used to supplement the electronic medical record system as needed. Patient information collected at ART initiation includes demographics (ie, sex, age, and employment) and clinical data (medical diagnoses, treatment regimens, and laboratory results).¹¹ Longitudinal clinical and laboratory data (CD4 counts, viral load), regimen changes, and other medical investigations are collected at each medical visit.

CD4+ T-cell lymphocyte counts are done using pan-leucogated CD4+ flow cytometry (FlowCount Fluorospheres, Beckman Coulter-Immuntotech, Villepinte, France) while HIV-1 RNA viral load tests are performed using NucliSENSEasyQ® HIV-1 assay (bioMérieux Clinical Diagnostics, Marcy l'Etoile, France). At TLC, treatment monitoring is done using CD4 counts and viral load tests between 4 and 7 months after initiation of a new regimen, thereafter at 6-month intervals or as clinically indicated under the 2004 HIV guidelines.¹⁴ However, as of April 2010, the monitoring schedule was shifted to 6 months after ART initiation and yearly thereafter.¹⁵ At the private clinic, monitoring is done every 3–4 months since the last scheduled visit or as clinically indicated. The National Health Laboratory Services (NHLS) are contracted to conduct laboratory services for TLC while the private clinic uses a private laboratory called AMPATH/Lancet Laboratory, a private pathology service available throughout South Africa.

The patients collect their antiretroviral drugs monthly or every 2 months when stable. Information is available on ART treatment outcomes including death, LTF (defined as failure to attend the clinic for more than 3 months since the last scheduled visit), and transfer or down referral to another facility. At both facilities, patients who miss scheduled visit dates are actively traced telephonically and misclassification is reduced by linking patients with a valid South African ID number to the South African National Vital Registration System to update their death status.⁸ The most recent linkage, for all sites using the electronic patient management system (TherapyEdge-HIV™; $n=10$), was conducted in April 2013 for research purposes.

The main exposure variable of the study was the type of clinic (private vs public) in which patients initiated ART. Sociodemographic variables and biological variables such as CD4 count and WHO clinical staging at ART initiation were also assessed. Body mass index (BMI; kg/m²) was used as a proxy for the nutritional status of patients at ART initiation.

Anemia was then categorized according to WHO guidelines as none ($\text{Hb} \geq 12.0$ g/dL for nonpregnant women and $\text{Hb} \geq 13.0$ g/dL for men), mild ($\text{Hb} 11.0\text{--}11.9$ g/dL for nonpregnant women and $11.0\text{--}12.9$ g/dL for men), moderate ($8.0\text{--}10.9$ g/dL), and severe ($\text{Hb} < 8.0$ g/dL).¹⁶ The WHO stage was determined either by physician classification or by conditions present at ART initiation.

The outcomes of the study included all-cause mortality and LTF, failure to suppress viral load (≥ 400 copies/mL) and CD4 count change (absolute difference in CD4 count from baseline to 12 months on treatment) at 12-month post-ART initiation. In patients that were alive and in care at 12-month post-ART initiation, the viral load or CD4 count results closest to 12 months but within 9 and 15 months of ART initiation were used in the analysis. We conducted a sensitivity analysis for those with a missing viral load at 12-month post-ART. In the first scenario, everyone with a missing value was assigned viral load < 400 copies/mL while in the second scenario everyone with a missing value was assigned viral load ≥ 400 copies/mL.

Statistical analysis

The data were exported from TherapyEdge-HIV™ into SAS 9.1 (SAS Institute Inc., Cary, NC, USA) and STATA 11™ (StataCorp LP (College Station, TX, USA) for the analysis. Baseline demographic, clinical, and immunological characteristics of patients at ART initiation at either clinic were compared. Continuous variables were described using means and standard deviations (parametric data) or medians and interquartile range (IQR; nonparametric data) and compared using Student's *t*-tests and Wilcoxon rank-sum test (Mann–Whitney), respectively. Categorical data were described using proportions and compared using Pearson's chi-square or Fischer's exact for sparse data.

Kaplan–Meier estimates were used to compare mortality and LTF between the two clinics. Cox proportional-hazard regression was used to identify predictors of mortality and LTF. Person-time started at ART initiation and ended at the earliest date of death, LTF, transfer, completion of 12 months of follow-up, or dataset closure (12/2013). Univariate analysis was used to select variables that were significant determinants of treatment outcomes at the $P < 0.20$ level of significance. These significant variables were then used to build the adjusted multivariate models. Confounding and effect modification were assessed using the Mantel–Haenszel method. Log-likelihood ratio tests were used to select the final model using an likelihood ratio chi-squared test $P \leq 0.05$. The assumption of proportionality of hazards was checked using Cox–Snell residual plots and Schoenfeld residuals tests.

Proportions were used to describe a virological response at 12-month post-ART initiation between the two facilities. Generalized estimating equations were used to assess predictors of failure to suppress viral load. Models were built and diagnostic tests performed as described earlier. The Wilcoxon rank-sum test was used to compare median absolute differences in CD4 count from baseline to 12-month post-ART initiation. Median change was calculated by subtracting the baseline CD4 count measurement from the CD4 count value at 12 months on ART.

This study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (protocol number M120863), and no patient consent was required by the committee, as all patient records/information were anonymized and de-identified prior to analysis.

Results

Baseline characteristics of the cohort

A total of 12,865 patients for the public and 610 patients for the private clinic were included in the analysis (Figure 1). Patients from the public clinic were similar to those in the private clinic in terms of sex, age at ART initiation, however, they were different in terms of CD4 count, educational level, employment status, WHO stage, initiating regimens, and nutritional status at baseline (Table 2). As expected, a higher proportion of private clinic patients were employed (86.4% vs 53.4%), presented earlier for ART initiation (WHO stages I or II 76.1% vs 58.5%), and recorded a higher median CD4 count 159 vs 113 cells/mm³ compared to the public clinic. However, patients enrolled in the public clinic recorded higher median BMI (BMI: 23.4 vs 21.6 kg/m²) compared to their counterparts.

Mortality at 12 months of ART

After 12 months on ART, 1,382/13,475 (10.3%) patients died in a median (IQR) follow-up of 0.4 (0.33–0.67) years. The overall incidence rate of mortality was 43 deaths/1,000 person years (pys), and (44 vs 20/1,000 pys; $P < 0.001$) stratified by clinic, respectively (public vs private). The risk of death was higher in the first 12 months of initiating ART for both facilities (91 vs 45/1,000 pys; $P < 0.001$), decreasing steadily with prolonged exposure to ART.

The type of clinic was found to be a significant predictor of mortality (Table 3). After adjusting for other covariates, private clinic patients had a lower risk of mortality compared to those in the public clinic (adjusted hazard ratio; aHR 0.50; 95% confidence interval [CI] 0.35–0.70). The risk of death increased with an increase in age at initiation. Patients aged above 50 years were almost two times more likely to die compared to young adults (18–29.9 years) (aHR 1.86; 95%

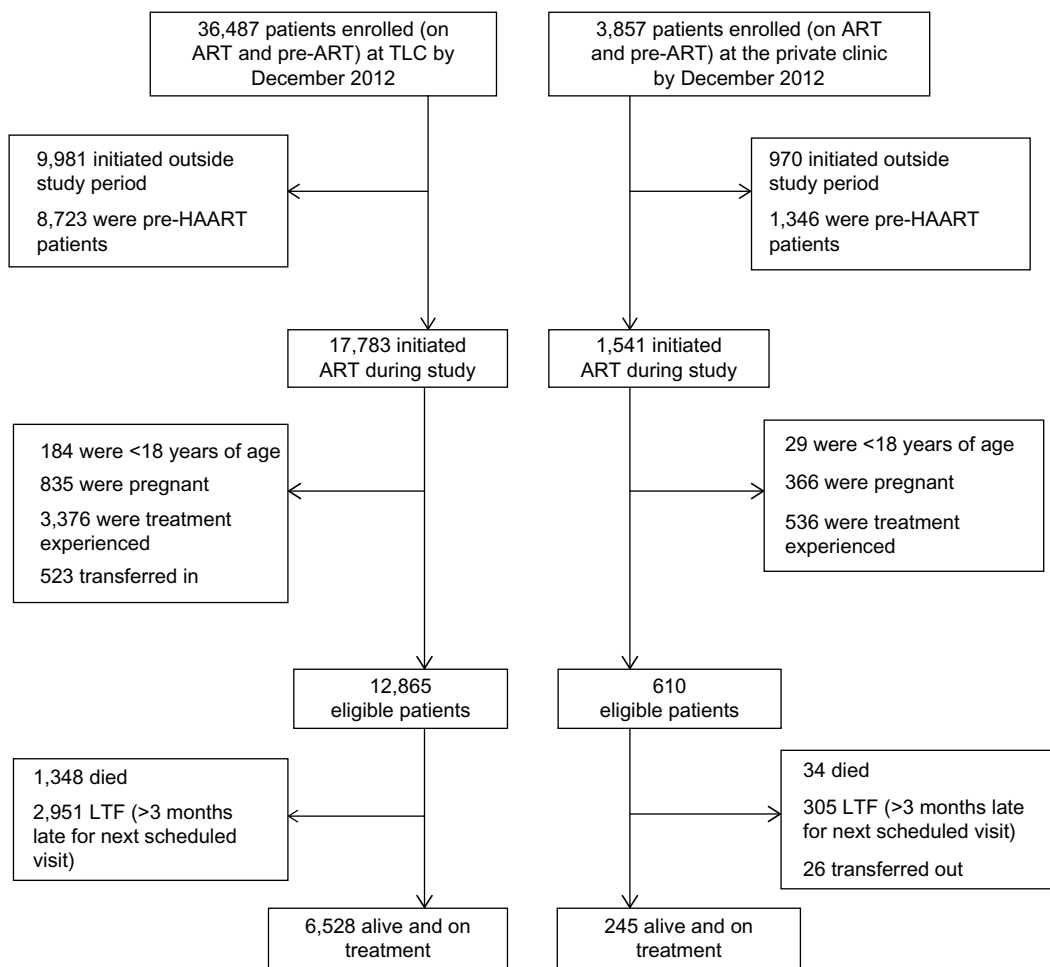


Figure 1 Cohort profile stratified by clinic type in December 2012.

Notes: This figure is a structured flow chart of how the final eligible study cohort was obtained from the original datasets from each clinic. It also shows the ART program losses (mortality and LTF) of each health facility.

Abbreviations: ART, antiretroviral therapy; TLC, Themba Lethu Clinic; HAART, highly active antiretroviral therapy; LTF, loss to follow-up.

CI 1.53–2.25). Males were more likely to die compared to females (aHR 1.20; 95% CI 1.07–1.34).

Patients initiating ART late (WHO stage III or IV) were more likely to die compared to those initiating treatment at the early stage of HIV (WHO stage I or II) (aHR 1.52; 95% CI 1.37–1.70). Initiating ART with a high CD4 count was protective against mortality as shown in Table 3. Underweight (BMI <18.5 kg/m²) patients at ART initiation were 1.8 times more likely to die compared to patients with a normal weight (BMI ≥18.5 kg/m²) (aHR 1.76; 95% CI 1.58–1.98). Similarly, patients with severe anemia (hemoglobin <8.0 g/dL) had a 50% greater risk of dying compared to those without anemia (aHR 1.47; 95% CI 1.31–1.64).

Loss to follow-up at 12 months of ART

Incidence rates were 95 vs 180 per 1,000 pys ($P < 0.001$), respectively, in the public and private clinic, respectively. Patients who initiated ART in the private sector were more

likely to be LTF (aHR 1.80; 95% CI 1.59–2.03; Table 3). Older patients were more likely to be retained on ART compared to young adults. For example, the ≥50 age group were less likely to be lost from the program compared to the 18–29 age group (aHR 0.70; 95% CI 0.61–0.80). Among the cohort, male vs female patients (aHR 1.45; 95% CI 1.35–1.55), and those with severe anemia (aHR 1.61; 95% CI 1.49–1.73) or low BMI <18.5 kg/m² (aHR 1.35; 95% CI 1.25–1.45) were at increased risk of being lost from care. In addition, lower CD4 count and less than primary level education were also significant predictors.

Immunological and virological responses to ART at 12 months of ART

By 12-month post-ART initiation, immunological and virological responses to ART were different between the clinics. A total of 10.5% (1,348/12,865) and 5.6% (34/610) in the public and private clinic had a detectable viral load at

Table 2 Baseline characteristics of HIV-positive patients on first-line antiretroviral therapy patients, stratified by clinic

Characteristic	Public, N=12,865	Private, N=610
Sex		
Female	7,644 (59.4%)	358 (58.7%)
Male	5,221 (40.6%)	252 (41.3%)
Age at initiation (years)		
Median (IQR)	37.4 (31.7–44.2)	36.9 (32.4–40.0)
18–29.9	2,331 (18.1%)	78 (12.8%)
30–39.9	5,484 (42.6%)	326 (53.4%)
40–49.9	3,498 (27.2%)	157 (25.8%)
≥50	1,552 (12.1%)	49 (8.0%)
Education		
Above primary level (≥ Grade 8)	11,206 (87.1%)	481 (78.9%)
Below primary level (< Grade 8)	467 (3.6%)	4 (0.7%)
Unknown	1,192 (9.3%)	125 (20.4%)
Employment		
Employed	6,866 (53.4%)	527 (86.4%)
Unemployed	5,999 (46.6%)	83 (13.6%)
CD4 count (cells/mm ³ blood)		
Median (IQR)	113 (43–189)	159 (66–251)
≤100	3,953 (30.7%)	97 (15.9%)
101–200	4,054 (31.5%)	159 (26.1%)
201–350	2,504 (19.5%)	276 (45.2%)
Missing	2,354 (18.3%)	78 (12.8%)
Log viral load		
Mean (SD)	9.9 (2.5)	10.5 (2.4)
BMI (kg/m ²)		
≥18.5	8,755 (68.1%)	306 (50.2%)
<18.5	2,574 (20.0%)	199 (32.6%)
Missing	1,536 (11.7%)	105 (17.2%)
Hemoglobin (g/dL)		
No anemia	2,844 (22.1%)	172 (28.2%)
Mild anemia	3,087 (24.0%)	186 (30.5%)
Moderate anemia	4,323 (33.6%)	169 (27.7%)
Severe anemia	939 (7.3%)	30 (4.9%)
Missing	1,672 (13.0%)	53 (8.7%)
WHO stage		
Stage I or II	7,525 (58.5%)	464 (76.1%)
Stage III or IV	4,260 (33.1%)	107 (17.5%)
Missing	1,080 (8.4%)	39 (6.4%)
Baseline ART regimen		
3TC/TDF/EFV	4,786 (37.2%)	26 (4.3%)
d4T/3TC/EFV	5,441 (42.3%)	4 (0.7%)
TDF/3TC/FTC	1,004 (7.8%)	232 (38.0%)
LPV/r/AZT/3TC	1,634 (12.7%)	348 (57.1%)
12-month outcomes		
Alive and in care	6,528 (50.7%)	245 (40.2%)
Dead	1,348 (10.5%)	34 (5.6%)
Loss to follow-up	2,951 (22.9%)	305 (50.0%)
Transferred out	2,038 (15.9%)	26 (4.2%)

Abbreviations: IQR, interquartile range; BMI, body mass index; WHO, World Health Organization; ART, antiretroviral therapy; 3TC, lamivudine; TDF, tenofovir; EFV, efavirenz; d4T, stavudine; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; AZT, zidovudine; SD, standard deviation.

12 months. Among those with a viral load at 12 months, private clinic patients were less likely to have a detectable viral load (adjusted relative risk [aRR]=0.65; 95% CI 0.49–0.88; Table 4). Compared to females, males had a greater risk of having a

detectable viral load at 12-month post-ART initiation (aRR 1.36; 95% CI 1.22–1.52). Similarly, underweight patients were more likely to have a detectable viral compared to patients with normal weight at baseline (aRR 1.23; 95% CI 1.09–1.39).

Among those alive and in care at 12 months, 45.0% (2,938/6,528) of the public clinic patients had a viral load at 12 months compared to 55.1% (135/245) patients at the private clinic. We conducted a sensitivity analysis to investigate the effect of missing viral load values on the inference estimates for our main exposure (ie, clinic type). We did not observe a difference in the direction of the effect of the exposure on virological outcomes at 12-month post-ART initiation, however, estimates were biased toward the null. That is unadjusted RR [uRR] 0.86; 95% CI 0.64–1.16, when missing values were assigned a viral load <400 copies/mL and uRR 0.83; 95% CI 0.77–0.90 when missing values were assigned a viral load ≥400 copies/mL.

The median CD4 change from baseline to 12 months of treatment was different between the sites, that is, median CD4 count change of 158 cells/mm³ (IQR 91–244) vs 184 cells/mm³ (IQR 101–300) in the public and private clinic ($P<0.001$), respectively. The proportion of patients with a CD4 change from baseline to 12-month post-ART initiation of less than 100 cells/mm³ was 3.2% for the private and 5.4% for the public clinic, respectively.

Discussion

We compared treatment outcomes, specifically all-cause mortality, LTF, failure to suppress viral load, and CD4 count change, among patients receiving HIV care and treatment at a public or private HIV clinic in Johannesburg, South Africa. In our study, we identified differences in treatment outcomes among study participants; mortality rates were found to be higher in the public clinic compared to the private clinic (44 vs 20/1,000 pys; $P<0.001$). However, LTF rates were lower in the public clinic (95 vs 180/1,000 pys; $P<0.001$). Patients receiving treatment in the private clinic had better immunological and virological outcomes at 12 months of ART.

We identified baseline predictors of all-cause mortality, LTF, failure to suppress viral load (≥400 copies/mL), and CD4 count change at 12-month post-ART initiation. The type of health facility in which patients received ART care, age at ART initiation, sex and baseline CD4 count, and nutritional status at baseline were identified as some of the significant predictors of treatment outcomes at 12 months on ART.

Mortality

Our findings showed that initiating treatment in the private clinic was protective against mortality. A South African

Table 3 Predictors of mortality and loss to follow-up at 12 months of ART among the cohort during the study period (July 2007–December 2012)

Factors at baseline	Mortality			Loss to follow-up		
	N ^a =1382, data shown as n/N (%)	Crude HR, (95% CI)	Adjusted HR, (95% CI)	N ^b =3,256, data shown as n/N (%)	Crude HR (95% CI)	Adjusted HR (95% CI)
Health facility						
Public	1,348/12,865 (10.5)	Reference	Reference	2,951/12,865 (22.9)	Reference	Reference
Private	34/610 (5.6)	0.49 (0.35–0.69)	0.50 (0.35–0.70)	305/610 (50.0)	1.91 (1.69–2.15)	1.80 (1.59–2.03)
Age at initiation (years)						
18–29.9	206/2,409 (8.6)	Reference	Reference	710/2,409 (29.5)	Reference	Reference
30–39.9	551/5,810 (9.5)	1.08 (0.92–1.27)	1.09 (0.93–1.28)	1,417/5,810 (24.4)	0.79 (0.73–0.87)	0.77 (0.70–0.86)
40–49.9	393/3,655 (10.8)	1.24 (1.05–1.47)	1.32 (1.11–1.57)	803/3,655 (21.9)	0.73 (0.66–0.81)	0.72 (0.65–0.80)
≥50	232/1,601 (14.5)	1.74 (1.45–2.11)	1.86 (1.53–2.25)	326/1,601 (20.4)	0.73 (0.64–0.83)	0.70 (0.61–0.80)
Sex						
Female	737/8,002 (9.2)	Reference	Reference	1,726/8,002 (21.6)	Reference	Reference
Male	645/5,473 (11.8)	1.34 (1.21–1.49)	1.20 (1.07–1.34)	1,530/5,473 (27.9)	1.40 (1.31–1.50)	1.45 (1.35–1.55)
Employment						
Unemployed	642/6,082 (10.6)	Reference	Reference	1,621/6,082 (26.7)	Reference	Reference
Employed	740/7,393 (10.0)	0.67 (0.60–0.74)	0.83 (0.74–1.92)	1,635/7,393 (22.1)	0.75 (0.70–0.80)	0.78 (0.73–0.84)
Education						
Above primary level (≥ Grade 8)	1,124/11,687 (9.6)	Reference	Reference	2,709/11,687 (23.2)	Reference	Reference
Below primary level (< Grade 8)	55/471 (11.7)	1.28 (0.98–1.68)	1.21 (0.92–1.59)	123/471 (26.1)	1.23 (1.02–1.47)	1.40 (1.16–1.68)
Unknown	203/1,317 (15.4)	1.82 (1.57–2.11)	1.66 (1.42–1.94)	424/1,317 (32.2)	1.31 (1.07–1.38)	1.42 (1.28–1.58)
WHO stage						
Stage I or II	705/7,989 (8.8)	Reference	Reference	1,973/7,989 (24.7)	Reference	Reference
Stage III or IV	545/4,367 (12.5)	2.11 (1.9–2.35)	1.52 (1.37–1.70)	1,048/4,367 (24.0)	1.22 (1.14–1.31)	1.03 (0.96–1.11)
CD4 count (cells/mm ³ blood)						
≤100	973/4,050 (24.0)	Reference	Reference	1,767/4,050 (43.6)	Reference	Reference
101–200	299/4,213 (7.1)	0.44 (0.38–0.50)	0.55 (0.48–0.63)	978/4,213 (23.2)	0.75 (0.69–0.81)	0.88 (0.81–0.95)
201–350	110/2,780 (4.0)	0.26 (0.21–0.31)	0.35 (0.29–0.43)	511/2,780 (18.4)	0.66 (0.59–0.72)	0.74 (0.67–0.82)
Hemoglobin (g/dL)						
No anemia	320/3,016 (7.3)	Reference	Reference	252/3,016 (8.4)	Reference	Reference
Mild anemia	410/3,273 (12.5)	1.56 (1.20–2.05)	1.25 (1.17–1.29)	373/3,273 (11.4)	1.27 (1.16–1.37)	1.22 (1.24–1.39)
Moderate anemia	481/4,492 (10.7)	1.34 (1.18–1.97)	1.13 (1.08–1.20)	489/4,492 (10.9)	1.19 (1.23–1.49)	1.13 (1.15–1.31)
Severe anemia	171/969 (17.7)	2.14 (1.90–2.35)	1.47 (1.31–1.64)	268/969 (27.7)	1.63 (1.52–1.75)	1.61 (1.49–1.73)
BMI (kg/m ²)						
≥18.5	699/9,061 (7.7)	Reference	Reference	1,868/9,061 (20.6)	Reference	Reference
<18.5	683/2,773 (24.6)	2.40 (2.15–2.66)	1.76 (1.58–1.98)	1,388/2,773 (50.0)	2.03 (1.89–2.18)	1.35 (1.25–1.45)

Notes: ^aNumber of patients that died during the study; ^bnumber of patients that were lost to follow-up. Reference = 1.00.

Abbreviations: ART, antiretroviral therapy; HR, hazard ratio; CI, confidence interval; WHO, World Health Organization; BMI, body mass index.

model using private physicians to treat and manage HIV using the South African DoH National ART treatment guidelines reported higher attrition rates in the private ART program.³ This could be because attrition was also inclusive of LTF in their study. We understand the difference in mortality rates between the two facilities to be a reflection of late entry to care (WHO clinical stage differences, differences in starting CD4 counts, and other comorbidities such as tuberculosis (TB) at ART initiation). Private clinic patients initiated treatment earlier, and did not have to wait until they met eligibility criteria which is a prerequisite in public sector ART programs. In addition, private patients may have had access to tertiary level care and alternative drug combinations that may result in greater tolerability, fewer side effects, better adherence,

and a commitment to ART. While the doctors in the public sector are bound to follow South African DoH National ART treatment guidelines, the private sector is less rigid and more permissive of individualism. Concerns have been raised over issues of noncompliance and poor regulation of prescribing standards in the private sector.^{5,18} Drugs that are reserved as second-line regimens in the public sector are often used as first-line regimens in the private sector. The variations in prescribing practices in the private sector may be determined by relations between pharmaceutical companies and physicians.¹⁸ There is a need for standardizing HIV care and treatment in both sectors to conserve and maximize first-line ART regimens and reduce the need for expensive second-line treatment. Public–private partnerships can address the

Table 4 Factors associated with failure to suppress viral load (≥ 400 copies/mL) after 12 months of ART during the study period (July 2007–December 2012)

Characteristic at baseline	N ^a =1,094, data shown as n/N (%)	Crude RR (95% CI)	Adjusted RR (95% CI)
Health facility			
Public	1,051/12,865 (8.2)	Reference	Reference
Private	43/610 (7.1)	0.71 (0.54–0.95)	0.65 (0.49–0.88)
Age at initiation (years)			
18–29.9	190/2,331 (8.2)	Reference	Reference
30–39.9	501/5,484 (9.1)	1.02 (0.87–1.18)	0.98 (0.84–1.14)
40–49.9	293/3,498 (8.4)	0.99 (0.84–1.17)	0.95 (0.80–0.99)
≥ 50	110/1,552 (0.1)	0.93 (0.75–1.16)	0.89 (0.71–1.10)
Sex			
Female	597/8,002 (7.5)	Reference	Reference
Male	497/5,473 (9.1)	1.35 (1.22–1.51)	1.36 (1.22–1.52)
Education			
Above primary level (\geq Grade 8)	999/11,687 (8.5)	Reference	Reference
Below primary level ($<$ Grade 8)	33/471 (7.0)	0.92 (0.67–1.27)	0.96 (0.70–1.32)
Unknown	62/1,317 (4.7)	0.80 (0.63–1.02)	0.80 (0.63–1.04)
CD4 count (cells/mm ³ blood)			
≤ 100	538/4,050 (13.3)	Reference	Reference
101–200	342/4,213 (8.1)	0.81 (0.72–0.92)	0.86 (0.76–0.97)
201–350	214/2,780 (7.7)	0.94 (0.81–1.08)	1.00 (0.87–1.16)
Employment			
Unemployed	456/6,082 (7.5)	Reference	Reference
Employed	638/7,393 (8.6)	0.83 (0.75–0.92)	1.08 (1.05–1.11)
WHO stage			
Stage I or II	752/7,989 (9.4)	Reference	Reference
Stage III or IV	342/4,367 (7.8)	0.99 (0.88–1.11)	0.90 (0.80–1.02)
Baseline BMI (kg/m ²)			
≥ 18.5	768/9,061 (8.5)	Reference	Reference
< 18.5	326/2,773 (11.8)	1.27 (1.14–1.44)	1.23 (1.09–1.39)
Baseline hemoglobin (g/dL)			
No anemia	271/3,016 (9.0)	Reference	Reference
Mild anemia	298/3,273 (9.1)	1.00 (0.87–1.05)	1.03 (0.92–1.13)
Moderate anemia	401/4,492 (8.9)	0.98 (0.79–1.11)	1.01 (0.96–1.19)
Severe anemia	124/969 (12.8)	1.12 (0.96–1.26)	1.14 (1.00–1.29)

Notes: ^aNumber of patients that had an elevated viral load (≥ 400 copies/mL after 12-month post-ART initiation). Reference = 1.00.

Abbreviations: ART, antiretroviral therapy; RR, risk ratio; CI, confidence interval; WHO, World Health Organization; BMI, body mass index.

issues of noncompliance and lack of standardized care in the private sector. This coalition also has the potential to address inadequacies of the public sector such as staff shortages, patient stigmatization, and drug shortages.¹⁹

For both facilities, mortality rates were high in the first 6 months of ART initiation. This observation is consistent with literature, with some authors reporting peaks in the first 12 months of ART.²⁰ This could also reflect the occurrence of immune reconstitution inflammatory syndrome (IRIS), which necessarily worsens the nature of disease and the response to treatment in the HIV-infected patient with opportunistic disease.^{21,22} This emphasizes the need for early identification of high-risk groups and early initiation of ART to prevent early mortality, especially in the public sector where the majority of patients initiate with advanced HIV.

We demonstrate that CD4 count, WHO clinical stage IV, and nutritional status (BMI and anemia) at ART initiation are significant predictors of mortality. These findings have also been reported elsewhere.^{20–25}

Loss to follow-up

The rate of LTF was higher in the private clinic, with rates increasing with ART duration. Research have shown that LTF is very common in the private sector, where patients with HIV often have to pay for all HIV-related services as well as treatment.^{4,5,26} The ability of patients within the South African private sector health program to continue to pay their monthly medical aid contributions may be difficult for those whose income and whose commitments to household debt are marginal at best. Unlike the public sector where patients

are usually obliged to go to one clinic, patients in the private sector may move to a different doctor for various reasons. This could also explain the high rates of loss from the private clinic in this study. In the public sector, intensive efforts are made to follow-up on patients before they are confirmed lost from the program.²⁷

Our results showed that retention rates increased with age (young adults are more likely to be lost from ART programs than older patients). Similar findings have been reported by other studies.^{23,26,28} This is consistent with the observation that younger, unemployed patients are likely to be lost from programs. Adults are likely to be employed, an important trait in the private health sector where there is a profound need for financial stability in ART provision. In the public sector, young unemployed adults may be lost due to lack of transport money to ART clinics. However, decentralization of care initiatives seems to be addressing such issues.²⁹

Immunological and virological responses at 12 months of ART

Better virological outcomes were observed in the private clinic as indicated by a greater proportion of patients that had a suppressed viral load at 12 months of ART in this clinic.

Higher absolute median CD4 changes were also recorded in the private clinic. Male patients were more likely to have poor virological outcomes. This finding suggests that stakeholders in ART programs need to incorporate male-friendly services targeted at this population to improve treatment outcomes. Close monitoring of the nutritional status of patients is important because our findings suggest that patients who were underweight or anemic were more likely to fail to suppress their viral load at 12 months on ART.

Limitations

The data used during the study were from one public ART clinic and one private ART clinic located in Johannesburg. The public clinic is a tertiary clinic supported by experts in HIV management. Hence, general outcomes would be expected to be better than an average public sector HIV clinic. Similarly, the private sector clinic is a dedicated HIV clinic run by an experienced HIV clinician. In addition, HIV management in the developed world is different from the limited resource countries. Consequently, the generalizability of findings to all settings is limited.

The findings of the study should be considered in light of other limitations namely small sample size of private patients relative to the public patients, missing data, and differences in data collection (data were prospectively collected after

2012 in the private clinic, while real-time data collection started as early as 2009 at TLC), differences in prescribing practices, CD4 count, and viral load monitoring between the two sectors and lack of data on adherence and viral resistance from both facilities. In addition, calculated vs actual LTF was determined, and this could have overestimated LTF rates in the study. At baseline, missing data ranged from 2.4% to 20.4% for the private clinic and from 8.4% to 18.3% for the public clinic. At 12 months, 45% (110/245) of patients in the private clinic and 55% (3,590/6,528) of patients in the public clinic did not have a viral load. We conducted a sensitivity analysis to investigate the effect of missing viral load values and did not observe a difference. In addition, we compared baseline characteristics of those with a missing viral load and those with a viral load at 12-month post-ART initiation and found no difference in age, education, baseline hemoglobin, and WHO stage ($P>0.05$) suggesting that viral load is missing at random and the results for those with a viral load measurement are representative of the entire study population. LTF may have led to a misclassification of mortality as LTF. Despite active patient tracing, mortality is substantially underestimated among HIV-positive patients lost from HIV treatment programs. Where possible and with valid national identification numbers, mortality was obtained and verified against the South African National Vital Registration system, which provides a more accurate assessment of mortality.^{8,30}

Conclusion

Findings from this study suggest that the type of health facility in which patients access ART can have an impact on treatment outcomes. In our study, both positive and negative outcomes were identified from either sector. Further research is recommended to provide more conclusive evidence.

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Disclosure

The authors report no conflicts of interest in this work.

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