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Citizenship status and engagement in HIV care: An observational cohort study to assess the association between reporting a national ID number and retention in public-sector HIV care in Johannesburg, South Africa

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Abstract

Objective: In many resource-limited settings, people from rural areas migrate to urban hubs in search of work. Thus, urban public-sector HIV clinics in South Africa (SA) often cater to both local residents and patients from other provinces and/or countries. The objective of this analysis was to compare programmatic treatment outcomes by citizenship status in an urban clinic in SA.

Setting: An urban public-sector HIV treatment facility in Johannesburg, SA.

Participants: We included all antiretroviral therapy (ART)-naïve, non-pregnant patients who initiated standard first-line treatment from January 2008-December 2013. 12,219 patients were included and 59.5% were female.

Primary outcome measure: Patients were followed from ART initiation until death, transfer, loss to follow-up (LTF), or dataset closure. We describe attrition (mortality and LTF) stratified by SA citizenship status (confirmed SA citizens [with national ID number], unconfirmed SA citizens [no ID], and foreign nationals) and model the risk of attrition using Cox proportional hazards regression.

Results: 70% of included patients were confirmed SA citizens, 19% were unconfirmed SA citizens, and 11% were foreign nationals. Unconfirmed SA citizens were far more likely to die or become LTF than other patients. A similar proportion of foreign nationals (18.2%) and confirmed SA citizens (17.7%) had left care at one year compared to 47.0% of unconfirmed SA citizens (aHR unconfirmed SA vs. confirmed SA: 2.65; 95% CI: 2.39-2.94). By the end of follow-up, 75.5% of unconfirmed SA citizens had left care, approximately twice that of any other group.

Conclusions: Unconfirmed SA citizens were more likely to drop out of care after ART initiation than other patients. Further research is needed to determine whether this observed attrition is representative of migration and/or self-transfer to another HIV clinic as such high rates of attrition pose challenges for the success of the national ART program.

Strengths and limitations of this study

- High retention in HIV care is necessary for treatment as prevention to have population level impacts on HIV transmission and incidence. However, retention in public-sector care may differ by an individual's citizenship status.

- Over 12,000 people living with HIV enrolled in an urban public-sector treatment program in South Africa were followed to investigate the relationship between citizenship status and retention and our results showed that patients who self-reported South African citizenship but did not have a national ID number recorded were less likely to be retained in care than citizens with an ID number or self-reported foreign nationals.

- We used data from a single public-sector facility which may limit generalizability and there may be some exposure misclassification as some foreign nationals may be incorrectly recorded as self-reported South African citizens without a national ID number. Additionally, we do not have information on migration patterns of individuals included in the study and can only speculate as to whether loss from care is indicative of population mobility.

- The use of a unique identifier for all patients seeking care in public-sector facilities, regardless of citizenship status, would improve our ability to trace patients through clinics and improve ascertainment of program-level as opposed to clinic-level retention in care.

Introduction

South Africa has one of the largest economies on the African continent, as measured by GDP, eclipsed only by Nigeria.[1] As such, people from all over the continent, and especially Sub-Saharan Africa, migrate to South Africa in search of employment.[2–4] Within South Africa itself, internal migration is common as residents of rural areas move to urban hubs or mining communities in hopes of improving their economic prospects.[3–5] As a result, public-sector antiretroviral therapy (ART) programs in urban centers such as Johannesburg cater to a wide variety of patients who have migrated from all over South Africa and the continent.

Based on the results from the HIV Prevention Trials Network (HPTN) 052 study, which found that earlier initiation of ART for treatment of HIV resulted in a 96% reduction in the risk of transmission to an uninfected partner, the concept of using antiretroviral treatment as HIV prevention has gained in popularity.[6] However, in order for treatment as prevention to have an impact on population-level transmission and incidence, retention in HIV treatment programs must remain high.[7,8] As a result, identifying patients at high risk of loss to follow-up is of utmost importance in order to target interventions that are most likely to succeed in retaining them in care.

Previous research has shown that while foreigners and/or migrants often experience as good clinical outcomes in HIV care as local residents, their risk of loss from care has been variable. Results from a study comparing outcomes among self-reported foreigners to self-reported South Africans in Johannesburg found that foreigners were less likely to have died or become lost to follow-up than South Africans (3.8% vs. 12.8%).[9] However, recent migrants in KwaZulu-Natal were 53% more likely to disengage from care than long term residents and migrant workers in Lesotho were over twice as likely to be lost to follow-up than non-migrant workers 3-6 months after ART initiation and more than 6 times as likely after more than 12 months on ART.[10,11] Thus, we sought to further investigate these relationships by evaluating whether attrition (death and loss to follow-up) from a large, outpatient HIV treatment facility in Johannesburg may be related to South African citizenship status.

Methods

Study Site

This analysis was conducted utilizing data from the Themba Lethu HIV Clinic, a large urban public-sector outpatient HIV treatment facility located with the Helen Joseph Hospital in Johannesburg, South Africa.

Since the roll-out of ART in the public-sector in 2004, Themba Lethu has seen approximately 30,000 patients and has initiated over 20,000 of those patients on ART.[12] Treatment provision at Themba Lethu follows the National Department of Health ART guidelines. Initially, treatment was offered to HIV-infected adult patients with a CD4 count <200 cells/mm^3 or World Health Organization (WHO) stage 3 disease.[13] The eligibility threshold was increased to 350 cells/mm^3 for pregnant women and patients co-infected with tuberculosis (TB) in 2010 and to all HIV-infected patients in 2011.[14,15] In 2013, pregnant women, those co-infected with TB, and those with WHO stage 3 or 4 disease could initiate ART regardless of their CD4 count.[16] The guidelines were most recently updated in 2015 and call for treatment initiation below a CD4 threshold of 500 cells/mm^3.[17]

While not a requirement to receive care, it is standard practice to ask all patients who present for care at Themba Lethu for their South African national identity number at their first visit. This information is collected along with other identifying details, including date of birth, country of birth, country of citizenship, physical address, and phone number. Approximately 60% of patients provide a valid ID number which can then be used to link lost to follow-up patients to the National Vital Registration System to improve ascertainment of mortality.[18] All demographic information along with routinely collected clinical data, including ART regimens, is entered into an electronic medical record called TherapyEdge-HIV^{TM} in real time by the clinician during the patient encounter. Laboratory results are downloaded directly into the system from databases maintained by the National Health Laboratory Service.[12]

Study Population

We conducted a retrospective cohort analysis using data collected prospectively as part of routine clinical care. All ART-naïve, adult (≥18 years old), non-pregnant patients who initiated a standard first-line ART regimen between January 2008 and December 2013 were included.

Study Variables

The primary exposure in this study was documentation of citizenship status in the electronic medical record, using three categories: Patients with a valid ID were categorized as confirmed South African if the 11th digit of the ID number identified the holder as a South African citizen (0). Few patients with a valid ID were identified as non-South African citizens (n=196) so were excluded from further analysis. Patients without a valid ID were categorized as either unconfirmed South Africans or as foreign nationals based on their self-reported country of citizenship.

Ascertainment of mortality as a reason for loss to follow-up (≥3 months late for a scheduled visit) is easier among patients with a valid South African ID number due to regular linkage to the National Vital Registration System. Thus, our primary outcome was attrition, defined as death and loss to follow-up combined, rather than mortality alone, as deceased patients without an ID whose death was not reported to the clinic would appear as lost to follow-up.

Patients were included in the analysis if they initiated a standard first-line ART regimen, defined as stavudine (d4T), zidovudine (AZT), or tenofovir (TDF), in combination with lamivudine (3TC) and efavirenz (EFV) or nevirapine (NVP). Patients on tenofovir could also have been prescribed emtricitabine (FTC) in place of lamivudine.[13,14] Potential confounders were identified *a priori* from the literature. The CD4 count recorded closest to ART initiation from 6 months prior to the date of ART initiation to 7 days after was considered to be the baseline CD4 count value. CD4 count was then categorized as <50 cells/mm^3, 50-99 cells/mm^3, 100-199 cells/mm^3, and ≥200 cells/mm^3. Standard categories were used for body mass index (BMI) and anemia was defined according to standards set by the WHO as severe (<8 g/dL), moderate (8-10 g/dL), mild (males: 11-12 g/dL; females: 11 g/dL), or none (males: ≥13 g/dL; females: ≥12 g/dL).[19] Year of ART initiation, age at ART initiation, co-infection with TB, and employment status were also considered.

Statistical Analysis

Patients were followed from the date of ART initiation until the earliest of death, loss to follow-up, transfer to another HIV treatment facility, or closing of the dataset (February 28, 2015). We present baseline demographic and clinical characteristics as simple proportions for categorical variables and as medians with interquartile ranges (IQR) for continuous variables. Crude Kaplan-Meier curves depicting the probability of remaining in care over time by 12 months and ever after ART initiation are presented stratified by citizenship status. Cox proportional hazards regression was utilized to estimate the association between citizenship status and the risk of attrition using a complete case analysis. Results are presented as hazard ratios (HR) with corresponding 95% confidence intervals (CI). Age, sex, and baseline CD4 count category were included as covariates in the adjusted model. Other baseline characteristics that were considered to be plausible confounders and were associated with both citizenship status and attrition ($p<0.2$) in crude analyses were also included.

As an additional analysis, we used multiple imputation using chained equations (MICE) to account for missing data on baseline CD4 count (6.5%), hemoglobin (8.4%), BMI (15.1%), and employment status (3.0%) and present these results in the accompanying appendix.

Ethical approval

Ethical approval for the use of de-identified data from the Themba Lethu Clinic was provided by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and the Institutional Review Board of Boston University.

Results

12,291 patients initiated a standard, first-line ART regimen between January 2008 and December 2013 and were included in this analysis. Of these, 59.5% were female, the median (IQR) age at ART initiation was 37.6 (31.7-44.4) years and the median (IQR) baseline CD4 count was 120 (46-195) cells/mm^3. Approximately 70% of patients were classified as confirmed South African citizens. Of the remaining 30% (n=3685), 62% were unconfirmed South African citizens who did not report an ID number and the remaining 38% self-identified as foreign nationals. Patients were followed for a median (IQR) of 28.4 (9.6-48.6) months from the date of ART initiation.

Unconfirmed citizens had poor clinical characteristics at baseline. They were more likely to have severe anemia (12.1%), WHO stage III or IV disease (15.8%), and be co-infected with TB (14.8%) than both confirmed citizens (severe anemia: 8.0%; WHO stage III or IV disease: 41.5%; TB co-infection: 12.1%) and foreign nationals (severe anemia: 6.7%; WHO stage III or IV disease: 32.6%; TB co-infection: 6.6%). Compared to foreign nationals, confirmed citizens also had a slightly lower median baseline CD4 count (101 vs. 137), and were less likely to be employed (45.9% vs. 58.6%) while foreign nationals were more likely to be under the age of 35 (53.6%) than confirmed (35.1%) and unconfirmed (43.5%) citizens (Table 1).

Unconfirmed South African citizens were far more likely to be dead or lost to follow-up at both 12 months and ever after ART initiation compared to all other patients. Using Kaplan-Meier analysis, 17.7% of confirmed citizens and 18.2% of foreign nationals had died or were lost to follow-up after 12 months on ART, compared to 47.0% of unconfirmed citizens. Likewise by the end of follow-up, 75.5% of unconfirmed citizens had died or dropped out of care, which was approximately twice the attrition experienced by any other group (Figure 1). However, we note that because anyone without a national ID

number cannot be linked to the national vital registration system, we cannot determine how much of this increase is related to death and how much is related to loss from care.

This relationship was explored further in both unadjusted and adjusted regression models. 9,451 patients had information available on all covariates of interest and were included in the models. Compared to confirmed South African citizens, at 12 months, unconfirmed South African citizens were almost 3 times as likely to die or drop out of care (HR: 2.94; 95% CI: 2.66-3.25), while a small protective effect was observed for foreign nationals (HR: 0.89; 95% CI: 0.74-1.06). The association was attenuated slightly when adjusted for baseline demographic and clinical characteristics but unconfirmed citizens remained over two and a half times more likely to have died or left care compared to confirmed citizens (aHR: 2.65; 95% CI: 2.39-2.94). By the end of follow-up, the increased risk for attrition from care remained for unconfirmed citizens (aHR: 2.68; 95% CI: 2.47-2.90) while a small protective effect continued to be observed for foreign nationals (aHR: 0.88; 95% CI: 0.77-1.00) (Table 2).

Multiple imputation

In addition to conducting a complete case analysis, we utilized multiple imputation to account for missing data in our analyses. This led to minor changes in our estimates, though the overall inference remained unchanged. At one year after ART initiation, unconfirmed citizens were over 2.5 times more likely to have died or become lost to follow-up as confirmed citizens (aHR: 2.72; 95% CI: 2.51-2.95) with a similar estimate observed at the end of follow-up (aHR: 2.70; 95% CI: 2.52-2.88). A small, though non-significant, effect was observed for foreign nationals compared to confirmed citizens at one year (aHR: 1.09; 95% CI: 0.95 – 1.25) while no association was observed at the end of follow-up (aHR: 0.97; 95% CI: 0.87 – 1.08) (Appendix).

Discussion

The national ID number is a ubiquitous part of everyday life for South African citizens. It is required as proof of identity for a number of situations, including accessing education and employment, applying for a driver's license or passport, voting, registering a mobile phone sim card, and for accessing household utility services such as water and electricity. Of the unconfirmed citizens at Themba Lethu, some may have known but declined to provide their ID number. Despite its importance, others may lack identification for various reasons: they may never have applied for an ID book due to not having the required documentation or they may have lost their ID book and not applied to have it re-issued.

Thus, our findings that unconfirmed South African citizens who did not report a national ID number are at increased risk of attrition from HIV care compared to confirmed South African citizens and foreign nationals raises numerous questions. First, why do these patients not have an ID number recorded? These patients may be truly undocumented South Africans who do not possess an ID number, they may have an ID number but chose to not report it in the clinic, or clinic staff may have failed to have asked for their number. While HIV care is provided free of charge to all who need it in the public sector in South Africa, the cost of other health services is determined via a means test. However, undocumented foreign nationals from non-Southern African Development Community (SADC) countries are excluded from the means test and patients are required to pay for other health related services in full, regardless of their actual ability to pay. In addition, the policy of free ART regardless of citizenship status in public-sector facilities has not always been uniformly followed, resulting in the need for directives from the Department of Health, issued in 2005 and 2008, to compel clinics to treat all people living with HIV who met eligibility criteria for ART initiation.[20,21] As a result of possible fear that they would be denied treatment for not being South African or, for undocumented immigrants deportation, we could speculate that some of the unconfirmed citizens may also be foreign nationals who felt compelled to claim South Africa as their country of citizenship. Thus, some of these patients may actually be foreign nationals misclassified as South Africans.

A second question that our findings raise is, why are these patients so much more likely to drop out of care after initiating treatment than any other group of patients? We considered that a survivor bias may exist in this cohort. If a patient does not provide their national ID number at their first visit, they may be asked for their ID number at later appointments. Patients who dropped out of care immediately after ART initiation would not have an opportunity to provide their national ID number at a later visit. However, we conducted a sensitivity analysis among only those individuals with at least one follow-up visit at least 7 days after ART initiation and our inferences remained unchanged. It is also possible that migration is a prominent factor in this group and that these patients may have left Johannesburg for another province or, if some are misclassified foreign nationals, they may have returned to their home country. Given that migrants have been shown to be at greater risk for loss from HIV care, it may be reasonable to speculate that some of the attrition observed among unconfirmed South African citizens is related to migration.[10,11]

Limitations to our analysis include the use of data obtained from a single urban public-sector facility which may limit generalizability, especially to rural areas of South Africa. In addition, as mentioned

previously, there may be exposure misclassification as some foreign nationals may be recorded as South African citizens. Likewise, there may also be some outcome misclassification as some of the attrition may be unreported self-transfers to other health facilities. Finally, we also do not have information on migration patterns of this cohort and thus can only speculate as to whether our findings are indicative of migration.

Conclusion

Our results highlight two important factors for the ongoing success of the South African national antiretroviral treatment program. First, targeted interventions designed to keep patients engaged in care is needed. Further research is warranted to understand more about self-reported South African citizens who do not present a national ID number in order to create interventions that will keep them in care. Secondly, introduction of a unique identifier for all patients on ART, regardless of citizenship status, is crucial for enabling the linkage of data across health facilities in order to identify self-transfers due to internal migration so that efforts can be focused on tracing patients who have truly dropped out of care and re-engage them in treatment.

Contributorship statement

KS designed the study, conducted the analysis, and drafted the manuscript. MPF supervised the study design, data analysis, and drafting of the paper. KC, GMR, WM, MM, LL, and IS provided input into the study design, analysis plan, and drafting of the paper.

Competing interests

The authors have no conflicts of interest to declare.

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Data sharing statement

The data is owned by the study site and National Department of Health (South Africa) and governed by the Human Research Ethics Committee (University of Witwatersrand, Johannesburg, South Africa). All relevant data is included in the paper and supplementary tables. The full data are available from the Health Economics and Epidemiology Research Office for researchers who meet the criteria for access to confidential data and have approval from the owners of the data (information@heroza.org).

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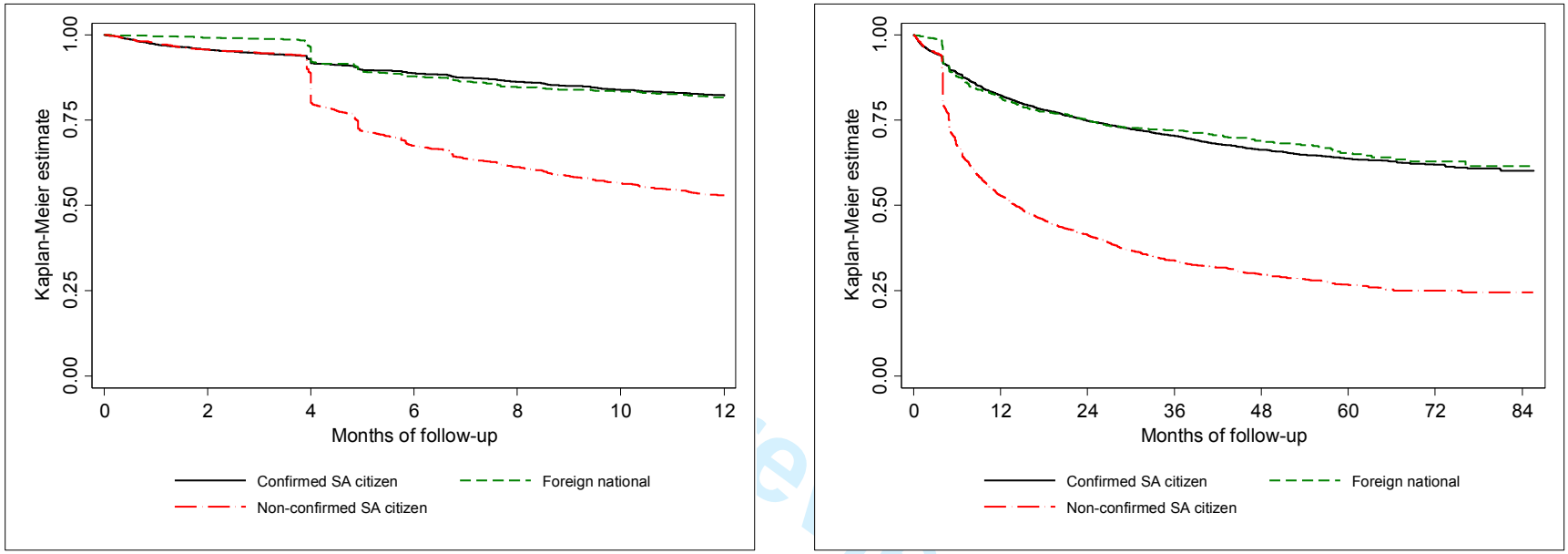
Table 1 – Demographic and clinical characteristics of patients who initiated antiretroviral therapy between January 2008 and December 2013 at the Themba Lethu Clinic in Johannesburg South Africa, stratified by documentation of South African citizenship

Characteristic	Total	Confirmed South African citizen	Unconfirmed South African citizen	Foreign National
Total	12219	8534	2292	1393
Year of ART initiation				
2008-09	4133 (33.8%)	2927 (34.3%)	985 (43.0%)	221 (15.9%)
2010-11	4791 (39.2%)	3324 (39.0%)	848 (37.0%)	619 (44.4%)
2012-13	3295 (27.0%)	2283 (26.8%)	459 (20.0%)	553 (39.7%)
Sex				
Male	4943 (40.5%)	3346 (39.2%)	1001 (43.7%)	596 (42.8%)
Female	7276 (59.5%)	5188 (60.8%)	1291 (56.3%)	797 (57.2%)
Age at ART initiation				
Median (IQR) N	37.6 (31.7 – 44.4)	38.4 (32.4 – 45.4)	36.5 (30.8 – 44.0)	34.3 (30.1 – 39.4)
<30	2227 (18.2%)	1390 (16.3%)	499 (21.8%)	338 (24.3%)
30-34.9	2511 (20.6%)	1605 (18.8%)	498 (21.7%)	408 (29.3%)
35-39.9	2610 (21.4%)	1826 (21.4%)	457 (19.9%)	327 (23.5%)
40-44.9	1993 (16.3%)	1482 (17.4%)	336 (14.7%)	175 (12.6%)
≥45	2878 (23.6%)	2231 (26.1%)	502 (21.9%)	145 (10.4%)
Employment status				
Missing	370 (3.0%)	222 (2.6%)	97 (4.2%)	51 (3.7%)
Employed	6691 (54.8%)	4822 (56.5%)	1053 (45.9%)	816 (58.6%)
Unemployed	5158 (42.2%)	3490 (40.9%)	1142 (49.8%)	526 (37.8%)
Baseline CD4 count (cells/mm^3)				
Median (IQR) N	120 (46 – 195)	122 (48 – 197)	101 (35 – 178)	137 (58.5 – 210)
Missing	789 (6.5%)	484 (5.7%)	188 (8.2%)	117 (8.4%)
<50	2991 (24.5%)	2047 (24.0%)	664 (29.0%)	280 (20.1%)
50-99	1947 (15.9%)	1366 (16.0%)	373 (16.3%)	208 (14.9%)
100-199	3791 (31.0%)	2683 (31.4%)	680 (29.7%)	428 (30.7%)
≥200	2701 (22.1%)	1954 (22.9%)	387 (16.9%)	360 (25.8%)
BMI at ART initiation (kg/m^2)				
Median (IQR) N	21.8 (19.3 – 25.3)	22.0 (19.3 – 25.7)	20.8 (18.6 – 23.8)	21.9 (19.7 – 24.9)
Missing	1839 (15.1%)	1088 (12.8%)	497 (21.7%)	254 (18.2%)
<18.5	1918 (15.7%)	1328 (15.6%)	432 (18.9%)	158 (11.3%)

18.5-24.9	5707 (46.7%)	3990 (46.8%)	1006 (43.9%)	711 (51.0%)
25-29.9	1812 (14.8%)	1364 (16.0%)	240 (10.5%)	208 (14.9%)
≥30	943 (7.7%)	764 (9.0%)	117 (5.1%)	62 (4.5%)
WHO Stage				
I/II	7037 (57.6%)	4993 (58.5%)	1105 (48.2%)	939 (67.4%)
III/IV	5182 (42.4%)	3541 (41.5%)	1187 (51.8%)	454 (32.6%)
Hemoglobin (g/dL) at ART initiation				
Median (IQR)	11.1 (9.5 – 12.6)	11.2 (9.6 – 12.6)	10.5 (8.9 – 12.2)	11.3 (9.8 – 12.8)
Anemia at ART initiation				
Missing	1027 (8.4%)	623 (7.3%)	262 (11.4%)	142 (10.2%)
No Anemia	3025 (24.8%)	2223 (26.1%)	420 (18.3%)	382 (27.4%)
Mild Anemia	2658 (21.8%)	1892 (22.2%)	457 (19.9%)	309 (22.2%)
Moderate Anemia	4455 (36.5%)	3113 (36.5%)	875 (38.2%)	467 (33.5%)
Severe Anemia	1054 (8.6%)	683 (8.0%)	278 (12.1%)	93 (6.7%)
Co-infected with tuberculosis at ART initiation				
Yes	1464 (12.0%)	1034 (12.1%)	338 (14.8%)	92 (6.6%)
First ART regimen[λ]				
TDF-3TC-EFV	5576 (45.6%)	3839 (45.0%)	914 (39.9%)	823 (59.1%)
d4T-3TC-EFV	4918 (40.3%)	3481 (40.8%)	1111 (48.5%)	326 (23.4%)
AZT-3TC-EFV	286 (45.6%)	202 (2.4%)	61 (2.7%)	23 (1.7%)
Other	1439 (11.8%)	1012 (11.9%)	206 (9.0%)	221 (15.9%)

[λ]TDF=Tenofovir; 3TC=lamivudine; EFV=efavirenz; d4T=stavudine; AZT=zidovudine; Other regimens are: TDF-3TC-NVP (nevirapine), AZT-3TC-NVP, TDF-EMT (emtricitabine)-EFV, TDF-EMT-NVP, and d4T-3TC-NVP

Figure 1 – Kaplan-Meier curves depicting time to death or loss to follow-up[Ÿ] at (a) 12 months and (b) ever after ART initiation among patients who initiated antiretroviral therapy between January 2008 and December 2013, stratified by SA citizenship status



[Ÿ]Large drop at approximately 4 months due to the definition of loss to follow-up which states that patients are only considered lost 3 months after a scheduled visit.

Table 2 – Unadjusted and adjusted estimates of attrition (death and loss to follow-up) at one-year and ever after ART initiation among 9,451 patients who initiated antiretroviral therapy between January 2008 and December 2013 at the Themba Lethu Clinic in Johannesburg, South Africa

Characteristic	One-year after ART initiation			Ever after ART initiation		
	Dead or LTF/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Dead or LTF/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Citizenship status						
Confirmed South African citizen	1019/6822 (14.9%)	**Reference**	**Reference**	1967/6822 (28.8%)	**Reference**	**Reference**
Unconfirmed South African citizen	605/1616 (37.4%)	2.94 (2.66, 3.25)	2.65 (2.39, 2.94)	959/1616 (59.3%)	2.92 (2.70, 3.15)	2.68 (2.47, 2.90)
Foreign national	138/1013 (13.6%)	0.89 (0.74, 1.06)	0.96 (0.80, 1.15)	254/1013 (25.1%)	0.85 (0.75, 0.97)	0.88 (0.77, 1.00)
Year of ART initiation						
2008-09	754/3669 (20.6%)	**Reference**	--	1505/3669 (41.0%)	**Reference**	**Reference**
2010-11	659/3744 (17.6%)	0.85 (0.77, 0.94)	--	1209/3744 (32.3%)	0.84 (0.78, 0.91)	1.03 (0.92, 1.14)
2012-13	349/2038 (17.1%)	0.81 (0.71, 0.92)	--	466/2038 (22.9%)	0.71 (0.64, 0.79)	1.01 (0.88, 1.15)
Sex						
Male	868/3779 (23.0%)	1.52 (1.39, 1.67)	1.50 (1.35, 1.66)	1525/3779 (40.4%)	1.51 (1.41, 1.62)	1.52 (1.41, 1.64)
Female	894/5672 (15.8%)	**Reference**	**Reference**	1655/5672 (29.2%)	**Reference**	**Reference**
Age at ART initiation						
<30	360/1689 (21.3%)	1.18 (1.02, 1.36)	1.03 (0.89, 1.20)	673/1689 (39.9%)	1.34 (1.21, 1.49)	1.22 (1.10, 1.37)
30-34.9	343/1957 (17.5%)	0.95 (0.83, 1.10)	0.84 (0.72, 0.97)	696/1957 (35.6%)	1.14 (1.03, 1.27)	1.06 (0.95, 1.18)
35-39.9	366/2034 (18.0%)	0.98 (0.85, 1.13)	0.89 (0.77, 1.02)	642/2034 (31.6%)	0.99 (0.89, 1.10)	0.93 (0.83, 1.03)
40-44.9	290/1541 (18.8%)	1.04 (0.89, 1.20)	0.99 (0.85, 1.15)	482/1541 (31.3%)	1.00 (0.89, 1.12)	0.97 (0.86, 1.09)
≥45	403/2230 (18.1%)	**Reference**	**Reference**	687/2230 (30.8%)	**Reference**	**Reference**
Employment status						
Employed	892/5489 (16.3%)	**Reference**	**Reference**	1605/5489 (29.2%)	**Reference**	**Reference**
Unemployed	870/3962 (22.0%)	1.41 (1.28, 1.54)	1.23 (1.11, 1.35)	1575/3962 (39.8%)	1.46 (1.36, 1.57)	1.32 (1.23, 1.42)
Baseline CD4 count (cells/mm^3)						
<50	675/2374 (28.4%)	2.79 (2.42, 3.22)	1.89 (1.62, 2.20)	1048/2374 (44.1%)	2.11 (1.90, 2.35)	1.56 (1.39, 1.75)
50-99	325/1618 (20.1%)	1.84 (1.56, 2.17)	1.37 (1.16, 1.63)	573/1618 (35.4%)	1.56 (1.38, 1.75)	1.24 (1.10, 1.41)
100-199	504/3264 (15.4%)	1.36 (1.17, 1.58)	1.19 (1.02, 1.38)	1042/3264 (31.9%)	1.35 (1.21, 1.50)	1.22 (1.10, 1.36)
≥200	258/2195 (11.8%)	**Reference**	**Reference**	517/2195 (23.6%)	**Reference**	**Reference**
BMI at ART initiation (kg/m^2)						
<18.5	534/1754 (30.4%)	1.87 (1.68, 2.08)	1.37 (1.23, 1.53)	836/1754 (47.7%)	1.65 (1.52, 1.79)	1.30 (1.19, 1.41)
18.5-24.9	948/5220 (18.2%)	**Reference**	**Reference**	1773/5220 (34.0%)	**Reference**	**Reference**
25-29.9	194/1637 (11.9%)	0.63 (0.54, 0.73)	0.83 (0.71, 0.98)	392/1637 (24.0%)	0.66 (0.60, 0.74)	0.85 (0.76, 0.96)
≥30	86/840 (10.2%)	0.54 (0.43, 0.67)	0.80 (0.64, 1.01)	179/840 (21.3%)	0.58 (0.50, 0.68)	0.83 (0.71, 0.97)
WHO Stage						
I/II	817/5483 (14.9%)	**Reference**	**Reference**	1564/5483 (28.5%)	**Reference**	**Reference**
III/IV	945/3968 (23.8%)	1.72 (1.57, 1.89)	1.12 (1.00, 1.25)	1616/3968 (40.7%)	1.52 (1.42, 1.63)	1.10 (1.02, 1.20)

Anemia at ART initiation						
No Anemia	330/2606 (12.7%)	**Reference**	**Reference**	713/2606 (27.4%)	**Reference**	**Reference**
Mild Anemia	367/2326 (15.8%)	1.27 (1.10, 1.48)	1.06 (0.91, 1.23)	725/2326 (31.2%)	1.13 (1.02, 1.26)	0.99 (0.89, 1.10)
Moderate Anemia	810/3751 (21.6%)	1.84 (1.62, 2.09)	1.47 (1.28, 1.69)	1382/3751 (36.8%)	1.43 (1.30, 1.56)	1.21 (1.09, 1.33)
Severe Anemia	255/768 (33.2%)	3.19 (2.71, 3.76)	2.24 (1.87, 2.69)	360/768 (46.9%)	2.10 (1.85, 2.38)	1.61 (1.40, 1.85)
Co-infected with tuberculosis at ART initiation						
No	1469/8297 (17.7%)	**Reference**	**Reference**	2662/8297 (32.1%)	**Reference**	**Reference**
Yes	293/1154 (25.4%)	1.50 (1.33, 1.70)	0.91 (0.79, 1.05)	518/1154 (44.9%)	1.48 (1.35, 1.63)	1.00 (0.90, 1.11)
First ART regimen[λ]						
TDF-3TC-EFV	688/3994 (17.2%)	**Reference**	**Reference**	1171/3994 (29.3%)	**Reference**	**Reference**
d4T-3TC-EFV	860/4132 (20.8%)	1.24 (1.12, 1.37)	0.97 (0.88, 1.08)	1651/4132 (40.0%)	1.27 (1.18, 1.37)	1.05 (0.95, 1.17)
AZT-3TC-EFV	40/182 (22.0%)	1.33 (0.97, 1.83)	1.22 (0.89, 1.69)	62/182 (34.1%)	1.20 (0.93, 1.55)	1.13 (0.86, 1.46)
Other	174/1143 (15.2%)	0.87 (0.74, 1.03)	0.94 (0.79, 1.11)	296/1143 (25.9%)	0.99 (0.87, 1.12)	1.02 (0.89, 1.17)

[λ]TDF=Tenofovir; 3TC=lamivudine; EFV=efavirenz; d4T=stavudine; AZT=zidovudine; Other regimens are: TDF-3TC-NVP (nevirapine), AZT-3TC-NVP, TDF-EMT (emtricitabine)-EFV, TDF-EMT-NVP, and d4T-3TC-NVP

Appendix - Unadjusted and adjusted estimates of attrition (death and loss to follow-up) at one-year and ever after ART initiation among 12,219 patients who initiated antiretroviral therapy between January 2008 and December 2013 at the Themba Lethu Clinic in Johannesburg, South Africa

Characteristic	One-year after ART initiation		Ever after ART initiation	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Citizenship status				
Confirmed South African citizen	**Reference**	**Reference**	**Reference**	**Reference**
Unconfirmed South African citizen	3.15 (2.90, 3.41)	2.72 (2.51, 2.95)	2.99 (2.80, 3.19)	2.70 (2.52, 2.88)
Foreign national	1.02 (0.89, 1.17)	1.09 (0.95, 1.25)	0.95 (0.85, 1.05)	0.97 (0.87, 1.08)
Year of ART initiation				
2008-09	**Reference**	--	**Reference**	**Reference**
2010-11	0.93 (0.86, 1.02)	--	0.91 (0.85, 0.97)	1.11 (1.01, 1.21)
2012-13	0.94 (0.86, 1.04)	--	0.84 (0.77, 0.91)	1.17 (1.06, 1.30)
Sex				
Male	1.51 (1.40, 1.63)	1.44 (1.32, 1.57)	1.48 (1.40, 1.57)	1.47 (1.37, 1.57)
Female	**Reference**	**Reference**	**Reference**	**Reference**
Age at ART initiation				
<30	1.07 (0.95, 1.20)	0.93 (0.83, 1.05)	1.27 (1.16, 1.39)	1.15 (1.05, 1.26)
30-34.9	0.94 (0.84, 1.05)	0.81 (0.72, 0.91)	1.10 (1.01, 1.21)	1.00 (0.92, 1.10)
35-39.9	0.98 (0.87, 1.09)	0.88 (0.78, 0.98)	0.98 (0.90, 1.08)	0.91 (0.83, 0.99)
40-44.9	0.95 (0.84, 1.07)	0.91 (0.80, 1.03)	0.95 (0.86, 1.05)	0.93 (0.84, 1.03)
≥45	**Reference**	**Reference**	**Reference**	**Reference**
Employment status				
Employed	**Reference**	**Reference**	**Reference**	**Reference**
Unemployed	1.59 (1.47, 1.71)	1.36 (1.26, 1.47)	1.55 (1.46, 1.64)	1.39 (1.30, 1.47)
Baseline CD4 count (cells/mm^3)				
<50	2.89 (2.55, 3.28)	1.85 (1.61, 2.11)	2.22 (2.03, 2.44)	1.59 (1.44, 1.75)
50-99	1.93 (1.68, 2.22)	1.39 (1.20, 1.60)	1.62 (1.46, 1.79)	1.27 (1.14, 1.42)
100-199	1.37 (1.20, 1.56)	1.18 (1.03, 1.35)	1.35 (1.23, 1.49)	1.23 (1.11, 1.35)
≥200	**Reference**	**Reference**	**Reference**	**Reference**
BMI at ART initiation (kg/m^2)				
<18.5	1.82 (1.64, 2.00)	1.31 (1.17, 1.45)	1.64 (1.52, 1.78)	1.27 (1.16, 1.38)
18.5-24.9	**Reference**	**Reference**	**Reference**	**Reference**
25-29.9	0.59 (0.51, 0.68)	0.79 (0.69, 0.92)	0.65 (0.59, 0.73)	0.85 (0.76, 0.95)
≥30	0.49 (0.40, 0.60)	0.75 (0.60, 0.92)	0.56 (0.49, 0.65)	0.81 (0.69, 0.94)
WHO Stage				
I/II	**Reference**	**Reference**	**Reference**	**Reference**
III/IV	1.97 (1.82, 2.12)	1.24 (1.13, 1.35)	1.67 (1.58, 1.78)	1.18 (1.10, 1.27)
Anemia at ART initiation				
No Anemia	**Reference**	**Reference**	**Reference**	**Reference**
Mild Anemia	1.40 (1.23, 1.60)	1.13 (0.98, 1.29)	1.22 (1.11, 1.33)	1.04 (0.94, 1.14)
Moderate Anemia	2.04 (1.82, 2.28)	1.53 (1.36, 1.74)	1.56 (1.43, 1.69)	1.27 (1.16, 1.39)
Severe Anemia	3.77 (3.28, 4.32)	2.36 (2.02, 2.75)	2.47 (2.22, 2.75)	1.74 (1.55, 1.96)
Co-infected with tuberculosis at ART initiation				
No	**Reference**	**Reference**	**Reference**	**Reference**
Yes	1.54 (1.39, 1.70)	0.90 (0.80, 1.00)	1.52 (1.40, 1.65)	0.99 (0.90, 1.08)
First ART regimen$^{\lambda}$				
TDF-3TC-EFV	**Reference**	**Reference**	**Reference**	**Reference**
d4T-3TC-EFV	1.15 (1.06, 1.24)	0.90 (0.83, 0.98)	1.20 (1.12, 1.28)	1.06 (0.98, 1.16)
AZT-3TC-EFV	1.31 (1.05, 1.65)	1.19 (0.94, 1.50)	1.22 (1.01, 1.48)	1.15 (0.95, 1.41)
Other	0.80 (0.70, 0.92)	0.91 (0.79, 1.04)	0.94 (0.85, 1.05)	1.02 (0.91, 1.14)

$^{\lambda}$TDF=Tenofovir; 3TC=lamivudine; EFV=efavirenz; d4T=stavudine; AZT=zidovudine; Other regimens are: TDF-3TC-NVP (nevirapine), AZT-3TC-NVP, TDF-EMT (emtricitabine)-EFV, TDF-EMT-NVP, and d4T-3TC-NVP

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Citizenship status and engagement in HIV care: An observational cohort study to assess the association between reporting a national ID number and retention in public-sector HIV care in Johannesburg, South Africa

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Primary Subject Heading:	HIV/AIDS
Secondary Subject Heading:	Health services research, Epidemiology, Global health, Infectious diseases, Public health
Keywords:	HIV & AIDS < INFECTIOUS DISEASES, loss to follow-up, mortality, attrition, citizenship, resource-limited settings

Citizenship status and engagement in HIV care: An observational cohort study to assess the association between reporting a national ID number and retention in public-sector HIV care in Johannesburg, South Africa

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Running head: Attrition from HIV care and documentation of citizenship

Word count: 2767

Abstract word count: 294

Key words: HIV, loss to follow-up, mortality, attrition, citizenship, resource-limited settings

Abstract

Objective: In many resource-limited settings, people from rural areas migrate to urban hubs in search of work. Thus, urban public-sector HIV clinics in South Africa (SA) often cater to both local residents and patients from other provinces and/or countries. The objective of this analysis was to compare programmatic treatment outcomes by citizenship status in an urban clinic in SA.

Setting: An urban public-sector HIV treatment facility in Johannesburg, SA.

Participants: We included all antiretroviral therapy (ART)-naïve, non-pregnant patients who initiated standard first-line treatment from January 2008-December 2013. 12,219 patients were included and 59.5% were female.

Primary outcome measure: Patients were followed from ART initiation until death, transfer, loss to follow-up (LTF), or dataset closure. We describe attrition (mortality and LTF) stratified by SA citizenship status (confirmed SA citizens [with national ID number], unconfirmed SA citizens [no ID], and foreign nationals) and model the risk of attrition using Cox proportional hazards regression.

Results: 70% of included patients were confirmed SA citizens, 19% were unconfirmed SA citizens, and 11% were foreign nationals. Unconfirmed SA citizens were far more likely to die or become LTF than other patients. A similar proportion of foreign nationals (18.2%) and confirmed SA citizens (17.7%) had left care at one year compared to 47.0% of unconfirmed SA citizens (aHR unconfirmed SA vs. confirmed SA: 2.68; 95% CI: 2.42-2.97). By the end of follow-up, 75.5% of unconfirmed SA citizens had left care, approximately twice that of any other group.

Conclusions: Unconfirmed SA citizens were more likely to drop out of care after ART initiation than other patients. Further research is needed to determine whether this observed attrition is representative of migration and/or self-transfer to another HIV clinic as such high rates of attrition pose challenges for the success of the national ART program.

Strengths and limitations of this study

- We used data from a single urban public-sector HIV treatment facility located within a tertiary hospital which may limit generalizability.
- There may be some exposure misclassification as some foreign nationals may be incorrectly recorded as self-reported South African citizens without a national ID number.
- We do not have information on migration patterns of individuals included in the study and can only speculate as to whether loss from care is indicative of population mobility.
- The study site uses a comprehensive electronic medical record in which laboratory results are uploaded directly into the system from the National Health Laboratory Service, reducing opportunities for missing data and/or data entry errors.
- Routine loss to follow-up tracing mitigates loss from ART care.

Introduction

South Africa has one of the largest economies on the African continent, as measured by GDP, eclipsed only by Nigeria.[1] As such, people from all over the continent, and especially Sub-Saharan Africa, migrate to South Africa in search of employment.[2–4] Within South Africa itself, internal migration is common as residents of rural areas move to urban hubs or mining communities in hopes of improving their economic prospects.[3–5] As a result, public-sector antiretroviral therapy (ART) programs in urban centers such as Johannesburg cater to a wide variety of patients who have migrated from all over South Africa and the continent.

Based on the results from the HIV Prevention Trials Network (HPTN) 052 study, which found that earlier initiation of ART for treatment of HIV resulted in a 96% reduction in the risk of transmission to an uninfected partner, the concept of using antiretroviral treatment as HIV prevention has gained in popularity.[6] However, in order for treatment as prevention to have an impact on population-level transmission and incidence, retention in HIV treatment programs must remain high.[7,8] As a result, identifying patients at high risk of loss to follow-up is of utmost importance in order to target interventions that are most likely to succeed in retaining them in care.

Previous research has shown that while foreigners and/or migrants often experience as good clinical outcomes in HIV care as local residents, their risk of loss from care has been variable. Results from a study comparing outcomes among self-reported foreigners to self-reported South Africans in Johannesburg found that foreigners were less likely to have died or become lost to follow-up than South Africans (3.8% vs. 12.8%).[9] However, recent migrants in KwaZulu-Natal were 53% more likely to disengage from care than long term residents and migrant workers in Lesotho were over twice as likely to be lost to follow-up than non-migrant workers 3-6 months after ART initiation and more than 6 times as likely after more than 12 months on ART.[10,11] Thus, we sought to further investigate these relationships by evaluating whether attrition (death and loss to follow-up) from a large, outpatient HIV treatment facility in Johannesburg may be related to South African citizenship status.

Methods

Study Site

This analysis was conducted utilizing data from the Themba Lethu HIV Clinic, a large urban public-sector outpatient HIV treatment facility located with the Helen Joseph Hospital in Johannesburg, South Africa.

Since the roll-out of ART in the public-sector in 2004, Themba Lethu has seen approximately 30,000 patients and has initiated over 20,000 of those patients on ART.[12] Treatment provision at Themba Lethu follows the National Department of Health ART guidelines. Initially, treatment was offered to HIV-infected adult patients with a CD4 count <200 cells/mm^3 or World Health Organization (WHO) stage 3 disease.[13] The eligibility threshold was increased to 350 cells/mm^3 for pregnant women and patients co-infected with tuberculosis (TB) in 2010 and to all HIV-infected patients in 2011.[14,15] In 2013, pregnant women, those co-infected with TB, and those with WHO stage 3 or 4 disease could initiate ART regardless of their CD4 count and in 2015, the treatment initiation threshold was raised to a CD4 count of 500 cells/mm^3.[16,17]

While not a requirement to receive care, it is standard practice to ask all patients who present for care at Themba Lethu for their South African national identity number at their first visit. This information is collected along with other identifying details, including date of birth, country of birth, country of citizenship, physical address, and phone number. Approximately 60% of patients provide a valid ID number which can then be used to link lost to follow-up patients to the National Vital Registration System to improve ascertainment of mortality.[18] For the remaining 40% of patients, vital status is primarily obtained through loss to follow-up tracing. Since 2007, loss to follow-up tracing has been a routine component of ART care at Themba Lethu. Clinic counselors make up to three attempts to contact patients who have missed a scheduled visit via the phone number recorded in their file. Until 2013, home-based visits may also have been conducted for patients who could not be contacted via phone. However, this service is no longer routinely available. All demographic information along with routinely collected clinical data, including ART regimens, is entered into an electronic medical record called TherapyEdge-HIV™ in real time by the clinician during the patient encounter. Laboratory results are downloaded directly into the system from databases maintained by the National Health Laboratory Service.[12]

Study Population

We conducted a retrospective cohort analysis using data collected prospectively as part of routine clinical care. All ART-naïve, adult (≥18 years old), non-pregnant patients who initiated a standard first-line ART regimen between January 2008 and December 2013 were included.

Study Variables

The primary exposure in this study was documentation of citizenship status in the electronic medical record, using three categories: Patients with a valid ID were categorized as confirmed South African if the 11th digit of the ID number identified the holder as a South African citizen (11th digit = 0). Few patients with a valid ID were identified as non-South African citizens (n=196) so were excluded from further analysis. Patients without a valid ID were categorized as either unconfirmed South Africans or as foreign nationals based on their self-reported country of citizenship.

Ascertainment of mortality as a reason for loss to follow-up (≥3 months late for a scheduled visit) is easier among patients with a valid South African ID number due to regular linkage to the National Vital Registration System. Thus, our primary outcome was attrition, defined as death and loss to follow-up combined, rather than mortality alone, as deceased patients without an ID whose death was not reported to the clinic would appear as lost to follow-up.

Patients were included in the analysis if they initiated a standard first-line ART regimen, defined as stavudine (d4T), zidovudine (AZT), or tenofovir (TDF), in combination with lamivudine (3TC) and efavirenz (EFV) or nevirapine (NVP). Patients on tenofovir could also have been prescribed emtricitabine (FTC) in place of lamivudine.[13,14] The CD4 count recorded closest to ART initiation from 6 months prior to the date of ART initiation to 7 days after was considered to be the baseline CD4 count value. CD4 count was then categorized as <50 cells/mm^3, 50-99 cells/mm^3, 100-199 cells/mm^3, and ≥200 cells/mm^3. Standard categories were used for body mass index (BMI) and anemia was defined according to standards set by the WHO as severe (<8 g/dL), moderate (8-10 g/dL), mild (males: 11-12 g/dL; females: 11 g/dL), or none (males: ≥13 g/dL; females: ≥12 g/dL).[19]

Statistical Analysis

Patients were followed from the date of ART initiation until the earliest of death, loss to follow-up, transfer to another HIV treatment facility, or closing of the dataset (February 28, 2015). We present baseline demographic and clinical characteristics as simple proportions for categorical variables and as medians with interquartile ranges (IQR) for continuous variables. Crude Kaplan-Meier curves depicting the probability of remaining in care over time by 12 months and ever after ART initiation are presented stratified by citizenship status. Cox proportional hazards regression was utilized to estimate the association between citizenship status and the risk of attrition using a complete case analysis. Results are presented as hazard ratios (HR) with corresponding 95% confidence intervals (CI). Age, sex, and baseline CD4 count category were included as covariates in the adjusted model. Other baseline

characteristics that were considered to be plausible confounders, including year of ART initiation, employment status, BMI, WHO stage, presence and severity of anemia, TB co-infection, and baseline ART regimen, and were associated with both citizenship status and attrition ($p<0.2$) in crude analyses were also included.

As an additional analysis, we used multiple imputation using chained equations (MICE) to account for missing data on baseline CD4 count (6.5%), hemoglobin (8.4%), BMI (15.1%), and employment status (3.0%) and present these results in the accompanying appendix.

Ethical approval

Ethical approval for the use of de-identified data from the Themba Lethu Clinic was provided by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand and the Institutional Review Board of Boston University.

Results

12,291 patients initiated a standard, first-line ART regimen between January 2008 and December 2013 and were included in this analysis. Of these, 59.5% were female, the median (IQR) age at ART initiation was 37.6 (31.7-44.4) years and the median (IQR) baseline CD4 count was 120 (46-195) cells/mm^3. Approximately 70% of patients were classified as confirmed South African citizens. Of the remaining 30% (n=3,685), 62% were unconfirmed South African citizens who did not report an ID number and the remaining 38% self-identified as foreign nationals. Patients were followed for a median (IQR) of 28.4 (9.6-48.6) months from the date of ART initiation.

Unconfirmed citizens had poor clinical characteristics at baseline. They were more likely to have severe anemia (12.1%), WHO stage III or IV disease (51.8%), and be co-infected with TB (14.8%) than both confirmed citizens (severe anemia: 8.0%; WHO stage III or IV disease: 41.5%; TB co-infection: 12.1%) and foreign nationals (severe anemia: 6.7%; WHO stage III or IV disease: 32.6%; TB co-infection: 6.6%). Compared to foreign nationals, unconfirmed citizens also had a slightly lower median baseline CD4 count (101 vs. 137), and were less likely to be employed (45.9% vs. 58.6%) while foreign nationals were more likely to be under the age of 35 (53.6%) than confirmed (35.1%) and unconfirmed (43.5%) citizens (Table 1).

Unconfirmed South African citizens were far more likely to be dead or lost to follow-up at both 12 months and ever after ART initiation compared to all other patients. Using Kaplan-Meier analysis, 17.7%

of confirmed citizens and 18.2% of foreign nationals had died or were lost to follow-up after 12 months on ART, compared to 47.0% of unconfirmed citizens. Likewise by the end of follow-up, 75.5% of unconfirmed citizens had died or dropped out of care, which was approximately twice the attrition experienced by any other group (Figure 1). However, we note that because individuals without a national ID number cannot be linked to the national vital registration system, we cannot determine how much of this increase is related to death and how much is related to loss from care.

This relationship was explored further in both unadjusted and adjusted regression models. 9,451 patients had information available on all covariates of interest and were included in the models. Compared to confirmed South African citizens, at 12 months, unconfirmed South African citizens were almost 3 times as likely to die or drop out of care (HR: 2.94; 95% CI: 2.66-3.25), while a small protective effect was observed for foreign nationals (HR: 0.89; 95% CI: 0.74-1.06). The association was attenuated slightly when adjusted for baseline demographic and clinical characteristics but unconfirmed citizens remained over two and a half times more likely to have died or left care compared to confirmed citizens (aHR: 2.68; 95% CI: 2.42-2.97). By the end of follow-up, the increased risk for attrition from care remained for unconfirmed citizens (aHR: 2.68; 95% CI: 2.47-2.90) while a small protective effect continued to be observed for foreign nationals (aHR: 0.88; 95% CI: 0.77-1.00) (Table 2).

Multiple imputation

In addition to conducting a complete case analysis, we utilized multiple imputation to account for missing data in our analyses. This led to minor changes in our estimates, though the overall inference remained unchanged. At one year after ART initiation, unconfirmed citizens were over 2.5 times more likely to have died or become lost to follow-up as confirmed citizens (aHR: 2.72; 95% CI: 2.51-2.95) with a similar estimate observed at the end of follow-up (aHR: 2.70; 95% CI: 2.52-2.88). A small, though non-significant, effect was observed for foreign nationals compared to confirmed citizens at one year (aHR: 1.09; 95% CI: 0.95 – 1.25) while no association was observed at the end of follow-up (aHR: 0.97; 95% CI: 0.87 – 1.08) (Appendix).

Discussion

The national ID number is a ubiquitous part of everyday life for South African citizens. It is required as proof of identity for a number of situations, including accessing education and employment, applying for a driver's license or passport, voting, registering a mobile phone sim card, and for accessing household utility services such as water and electricity. Of the unconfirmed citizens at Themba Lethu, some may

have known but declined to provide their ID number. Despite its importance, others may lack identification for various reasons: they may never have applied for an ID book due to not having the required documentation or they may have lost their ID book and not applied to have it re-issued.

Thus, our findings that unconfirmed South African citizens who did not report a national ID number are at increased risk of attrition from HIV care compared to confirmed South African citizens and foreign nationals raises numerous questions. First, why do these patients not have an ID number recorded? These patients may be truly undocumented South Africans who do not possess an ID number, they may have an ID number but chose to not report it in the clinic, or clinic staff may have failed to have asked for their number. While HIV care is provided free of charge to all who need it in the public sector in South Africa, the cost of other health services is determined via a means test. However, undocumented foreign nationals from non-Southern African Development Community (SADC) countries are excluded from the means test and patients are required to pay for other health related services in full, regardless of their actual ability to pay. In addition, the policy of free ART regardless of citizenship status in public-sector facilities has not always been uniformly followed, resulting in the need for directives from the Department of Health, issued in 2005 and 2008, to compel clinics to treat all people living with HIV who met eligibility criteria for ART initiation.[20,21] As a result of possible fear that they would be denied treatment for not being South African or, for undocumented immigrants deportation, we could speculate that some of the unconfirmed citizens may also be foreign nationals who felt compelled to claim South Africa as their country of citizenship. Thus, some of these patients may actually be foreign nationals misclassified as South Africans.

A second question that our findings raise is, why are these patients so much more likely to drop out of care after initiating treatment than any other group of patients? We considered that a survivor bias may exist in this cohort. If a patient does not provide their national ID number at their first visit, they may be asked for their ID number at later appointments. Patients who dropped out of care immediately after ART initiation would not have an opportunity to provide their national ID number at a later visit. However, we conducted a sensitivity analysis among only those individuals with at least one follow-up visit at least 7 days after ART initiation and our inferences remained unchanged. It is also possible that migration is a prominent factor in this group and that these patients may have left Johannesburg for another province or, if some are misclassified foreign nationals, they may have returned to their home country. Given that migrants have been shown to be at greater risk for loss from HIV care, it may be

reasonable to speculate that some of the attrition observed among unconfirmed South African citizens is related to migration.[10,11]

Limitations to our analysis include the use of data obtained from a single urban public-sector facility which may limit generalizability, especially to rural areas of South Africa. In addition, as mentioned previously, there may be exposure misclassification as some foreign nationals may be recorded as South African citizens. Likewise, there may also be some outcome misclassification as some of the attrition may be unreported self-transfers to other health facilities. Finally, we also do not have information on migration patterns of this cohort and thus can only speculate as to whether our findings are indicative of migration.

Conclusion

Our results highlight two important factors for the ongoing success of the South African national antiretroviral treatment program. First, targeted interventions designed to keep patients engaged in care is needed. Further research is warranted to understand more about self-reported South African citizens who do not present a national ID number in order to create interventions that will keep them in care. Secondly, introduction of a unique identifier for all patients on ART, regardless of citizenship status, is crucial for enabling the linkage of data across health facilities in order to identify self-transfers due to internal migration so that efforts can be focused on tracing patients who have truly dropped out of care and re-engage them in treatment.

Contributorship statement

KS designed the study, conducted the analysis, and drafted the manuscript. MPF supervised the study design, data analysis, and drafting of the paper. KC, GMR, WM, MM, LL, and IS provided input into the study design, analysis plan, and drafting of the paper.

Competing interests

The authors have no conflicts of interest to declare.

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Data sharing statement

The data is owned by the study site and National Department of Health (South Africa) and governed by the Human Research Ethics Committee (University of Witwatersrand, Johannesburg, South Africa). All relevant data is included in the paper and supplementary tables. The full data are available from the Health Economics and Epidemiology Research Office for researchers who meet the criteria for access to confidential data and have approval from the owners of the data (information@heroza.org).

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Table 1 – Demographic and clinical characteristics of patients who initiated antiretroviral therapy between January 2008 and December 2013 at the Themba Lethu Clinic in Johannesburg South Africa, stratified by documentation of South African citizenship

Characteristic	Total	Confirmed South African Citizen	Unconfirmed South African Citizen	Foreign National
Total	12219	8534	2292	1393
Year of ART initiation				
2008-09	4133 (33.8%)	2927 (34.3%)	985 (43.0%)	221 (15.9%)
2010-11	4791 (39.2%)	3324 (39.0%)	848 (37.0%)	619 (44.4%)
2012-13	3295 (27.0%)	2283 (26.8%)	459 (20.0%)	553 (39.7%)
Sex				
Male	4943 (40.5%)	3346 (39.2%)	1001 (43.7%)	596 (42.8%)
Female	7276 (59.5%)	5188 (60.8%)	1291 (56.3%)	797 (57.2%)
Age at ART initiation				
Median (IQR) N	37.6 (31.7 – 44.4)	38.4 (32.4 – 45.4)	36.5 (30.8 – 44.0)	34.3 (30.1 – 39.4)
<30	2227 (18.2%)	1390 (16.3%)	499 (21.8%)	338 (24.3%)
30-34.9	2511 (20.6%)	1605 (18.8%)	498 (21.7%)	408 (29.3%)
35-39.9	2610 (21.4%)	1826 (21.4%)	457 (19.9%)	327 (23.5%)
40-44.9	1993 (16.3%)	1482 (17.4%)	336 (14.7%)	175 (12.6%)
≥45	2878 (23.6%)	2231 (26.1%)	502 (21.9%)	145 (10.4%)
Employment status				
Missing	370 (3.0%)	222 (2.6%)	97 (4.2%)	51 (3.7%)
Employed	6691 (54.8%)	4822 (56.5%)	1053 (45.9%)	816 (58.6%)
Unemployed	5158 (42.2%)	3490 (40.9%)	1142 (49.8%)	526 (37.8%)
Baseline CD4 count (cells/mm^3)				
Median (IQR) N	120 (46 – 195)	122 (48 – 197)	101 (35 – 178)	137 (58.5 – 210)
Missing	789 (6.5%)	484 (5.7%)	188 (8.2%)	117 (8.4%)
<50	2991 (24.5%)	2047 (24.0%)	664 (29.0%)	280 (20.1%)
50-99	1947 (15.9%)	1366 (16.0%)	373 (16.3%)	208 (14.9%)
100-199	3791 (31.0%)	2683 (31.4%)	680 (29.7%)	428 (30.7%)
≥200	2701 (22.1%)	1954 (22.9%)	387 (16.9%)	360 (25.8%)
BMI at ART initiation (kg/m^2)				
Median (IQR) N	21.8 (19.3 – 25.3)	22.0 (19.3 – 25.7)	20.8 (18.6 – 23.8)	21.9 (19.7 – 24.9)
Missing	1839 (15.1%)	1088 (12.8%)	497 (21.7%)	254 (18.2%)
<18.5	1918 (15.7%)	1328 (15.6%)	432 (18.9%)	158 (11.3%)
18.5-24.9	5707 (46.7%)	3990 (46.8%)	1006 (43.9%)	711 (51.0%)
25-29.9	1812 (14.8%)	1364 (16.0%)	240 (10.5%)	208 (14.9%)
≥30	943 (7.7%)	764 (9.0%)	117 (5.1%)	62 (4.5%)
WHO Stage				
I/II	7037 (57.6%)	4993 (58.5%)	1105 (48.2%)	939 (67.4%)
III/IV	5182 (42.4%)	3541 (41.5%)	1187 (51.8%)	454 (32.6%)
Hemoglobin (g/dL) at ART initiation				
Median (IQR)	11.1 (9.5 – 12.6)	11.2 (9.6 – 12.6)	10.5 (8.9 – 12.2)	11.3 (9.8 – 12.8)
Anemia at ART initiation				
Missing	1027 (8.4%)	623 (7.3%)	262 (11.4%)	142 (10.2%)

No Anemia	3025 (24.8%)	2223 (26.1%)	420 (18.3%)	382 (27.4%)
Mild Anemia	2658 (21.8%)	1892 (22.2%)	457 (19.9%)	309 (22.2%)
Moderate Anemia	4455 (36.5%)	3113 (36.5%)	875 (38.2%)	467 (33.5%)
Severe Anemia	1054 (8.6%)	683 (8.0%)	278 (12.1%)	93 (6.7%)
Co-infected with tuberculosis at ART initiation				
Yes	1464 (12.0%)	1034 (12.1%)	338 (14.8%)	92 (6.6%)
First ART regimen[λ]				
TDF-3TC-EFV	5576 (45.6%)	3839 (45.0%)	914 (39.9%)	823 (59.1%)
d4T-3TC-EFV	4918 (40.3%)	3481 (40.8%)	1111 (48.5%)	326 (23.4%)
AZT-3TC-EFV	286 (2.3%)	202 (2.4%)	61 (2.7%)	23 (1.7%)
Other	1439 (11.8%)	1012 (11.9%)	206 (9.0%)	221 (15.9%)

[λ]TDF=Tenofovir; 3TC=lamivudine; EFV=efavirenz; d4T=stavudine; AZT=zidovudine; Other regimens are: TDF-3TC-NVP (nevirapine), AZT-3TC-NVP, TDF-EMT (emtricitabine)-EFV, TDF-EMT-NVP, and d4T-3TC-NVP

Table 2 – Unadjusted and adjusted estimates of attrition (death and loss to follow-up) at one-year and ever after ART initiation among 9,451 patients who initiated antiretroviral therapy between January 2008 and December 2013 at the Themba Lethu Clinic in Johannesburg, South Africa

Characteristic	One-year after ART initiation			Ever after ART initiation		
	Dead or LTF/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Dead or LTF/N (%)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Citizenship status						
Confirmed South African citizen	1019/6822 (14.9%)	**Reference**	**Reference**	1967/6822 (28.8%)	**Reference**	**Reference**
Unconfirmed South African citizen	605/1616 (37.4%)	2.94 (2.66, 3.25)	2.68 (2.42, 2.97)	959/1616 (59.3%)	2.92 (2.70, 3.15)	2.68 (2.47, 2.90)
Foreign national	138/1013 (13.6%)	0.89 (0.74, 1.06)	0.95 (0.79, 1.14)	254/1013 (25.1%)	0.85 (0.75, 0.97)	0.88 (0.77, 1.00)
Year of ART initiation						
2008-09	754/3669 (20.6%)	**Reference**	**Reference**	1505/3669 (41.0%)	**Reference**	**Reference**
2010-11	659/3744 (17.6%)	0.85 (0.77, 0.94)	1.04 (0.90, 1.19)	1209/3744 (32.3%)	0.84 (0.78, 0.91)	1.03 (0.92, 1.14)
2012-13	349/2038 (17.1%)	0.81 (0.71, 0.92)	1.22 (1.03, 1.44)	466/2038 (22.9%)	0.71 (0.64, 0.79)	1.01 (0.88, 1.15)
Sex						
Male	868/3779 (23.0%)	1.52 (1.39, 1.67)	1.49 (1.34, 1.65)	1525/3779 (40.4%)	1.51 (1.41, 1.62)	1.52 (1.41, 1.64)
Female	894/5672 (15.8%)	**Reference**	**Reference**	1655/5672 (29.2%)	**Reference**	**Reference**
Age at ART initiation						
<30	360/1689 (21.3%)	1.18 (1.02, 1.36)	1.04 (0.90, 1.21)	673/1689 (39.9%)	1.34 (1.21, 1.49)	1.22 (1.10, 1.37)
30-34.9	343/1957 (17.5%)	0.95 (0.83, 1.10)	0.84 (0.72, 0.97)	696/1957 (35.6%)	1.14 (1.03, 1.27)	1.06 (0.95, 1.18)
35-39.9	366/2034 (18.0%)	0.98 (0.85, 1.13)	0.89 (0.77, 1.03)	642/2034 (31.6%)	0.99 (0.89, 1.10)	0.93 (0.83, 1.03)
40-44.9	290/1541 (18.8%)	1.04 (0.89, 1.20)	0.99 (0.85, 1.15)	482/1541 (31.3%)	1.00 (0.89, 1.12)	0.97 (0.86, 1.09)
≥45	403/2230 (18.1%)	**Reference**	**Reference**	687/2230 (30.8%)	**Reference**	**Reference**
Employment status						
Employed	892/5489 (16.3%)	**Reference**	**Reference**	1605/5489 (29.2%)	**Reference**	**Reference**
Unemployed	870/3962 (22.0%)	1.41 (1.28, 1.54)	1.23 (1.11, 1.35)	1575/3962 (39.8%)	1.46 (1.36, 1.57)	1.32 (1.23, 1.42)
Baseline CD4 count (cells/mm^3)						
<50	675/2374 (28.4%)	2.79 (2.42, 3.22)	1.93 (1.65, 2.25)	1048/2374 (44.1%)	2.11 (1.90, 2.35)	1.56 (1.39, 1.75)
50-99	325/1618 (20.1%)	1.84 (1.56, 2.17)	1.40 (1.18, 1.67)	573/1618 (35.4%)	1.56 (1.38, 1.75)	1.24 (1.10, 1.41)
100-199	504/3264 (15.4%)	1.36 (1.17, 1.58)	1.22 (1.04, 1.42)	1042/3264 (31.9%)	1.35 (1.21, 1.50)	1.22 (1.10, 1.36)
≥200	258/2195 (11.8%)	**Reference**	**Reference**	517/2195 (23.6%)	**Reference**	**Reference**
BMI at ART initiation (kg/m^2)						
<18.5	534/1754 (30.4%)	1.87 (1.68, 2.08)	1.37 (1.22, 1.53)	836/1754 (47.7%)	1.65 (1.52, 1.79)	1.30 (1.19, 1.41)
18.5-24.9	948/5220 (18.2%)	**Reference**	**Reference**	1773/5220 (34.0%)	**Reference**	**Reference**
25-29.9	194/1637 (11.9%)	0.63 (0.54, 0.73)	0.83 (0.71, 0.98)	392/1637 (24.0%)	0.66 (0.60, 0.74)	0.85 (0.76, 0.96)
≥30	86/840 (10.2%)	0.54 (0.43, 0.67)	0.80 (0.64, 1.01)	179/840 (21.3%)	0.58 (0.50, 0.68)	0.83 (0.71, 0.97)
WHO Stage						
I/II	817/5483 (14.9%)	**Reference**	**Reference**	1564/5483 (28.5%)	**Reference**	**Reference**
III/IV	945/3968 (23.8%)	1.72 (1.57, 1.89)	1.13 (1.01, 1.27)	1616/3968 (40.7%)	1.52 (1.42, 1.63)	1.10 (1.02, 1.20)

Anemia at ART initiation						
No Anemia	330/2606 (12.7%)	**Reference**	**Reference**	713/2606 (27.4%)	**Reference**	**Reference**
Mild Anemia	367/2326 (15.8%)	1.27 (1.10, 1.48)	1.06 (0.91, 1.24)	725/2326 (31.2%)	1.13 (1.02, 1.26)	0.99 (0.89, 1.10)
Moderate Anemia	810/3751 (21.6%)	1.84 (1.62, 2.09)	1.46 (1.27, 1.68)	1382/3751 (36.8%)	1.43 (1.30, 1.56)	1.21 (1.09, 1.33)
Severe Anemia	255/768 (33.2%)	3.19 (2.71, 3.76)	2.23 (1.85, 2.67)	360/768 (46.9%)	2.10 (1.85, 2.38)	1.61 (1.40, 1.85)
Co-infected with tuberculosis at ART initiation						
No	1469/8297 (17.7%)	**Reference**	**Reference**	2662/8297 (32.1%)	**Reference**	**Reference**
Yes	293/1154 (25.4%)	1.50 (1.33, 1.70)	0.92 (0.80, 1.06)	518/1154 (44.9%)	1.48 (1.35, 1.63)	1.00 (0.90, 1.11)
First ART regimen[λ]						
TDF-3TC-EFV	688/3994 (17.2%)	**Reference**	**Reference**	1171/3994 (29.3%)	**Reference**	**Reference**
d4T-3TC-EFV	860/4132 (20.8%)	1.24 (1.12, 1.37)	1.03 (0.90, 1.19)	1651/4132 (40.0%)	1.27 (1.18, 1.37)	1.05 (0.95, 1.17)
AZT-3TC-EFV	40/182 (22.0%)	1.33 (0.97, 1.83)	1.26 (0.90, 1.74)	62/182 (34.1%)	1.20 (0.93, 1.55)	1.13 (0.86, 1.46)
Other	174/1143 (15.2%)	0.87 (0.74, 1.03)	0.91 (0.76, 1.09)	296/1143 (25.9%)	0.99 (0.87, 1.12)	1.02 (0.89, 1.17)

[λ]TDF=Tenofovir; 3TC=lamivudine; EFV=efavirenz; d4T=stavudine; AZT=zidovudine; Other regimens are: TDF-3TC-NVP (nevirapine), AZT-3TC-NVP, TDF-EMT (emtricitabine)-EFV, TDF-EMT-NVP, and d4T-3TC-NVP

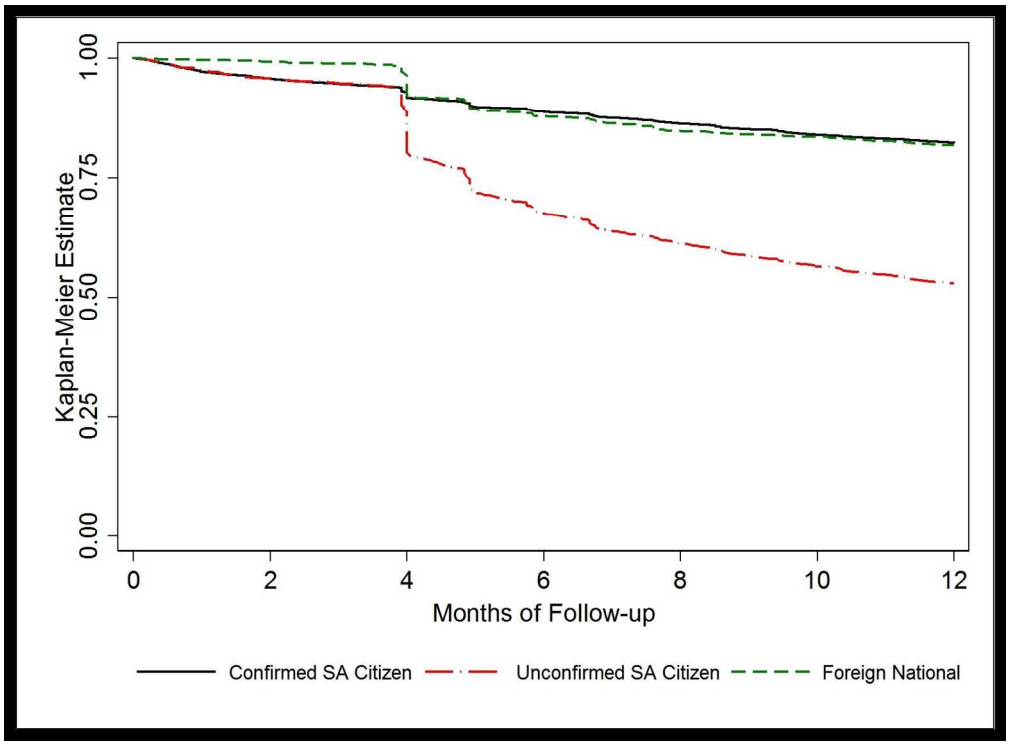

Figure 1a – Kaplan-Meier curve depicting time to death or loss to follow-up at 12 months after ART initiation among patients who initiated antiretroviral therapy between January 2008 and December 2013, stratified by SA citizenship status

142x104mm (300 x 300 DPI)

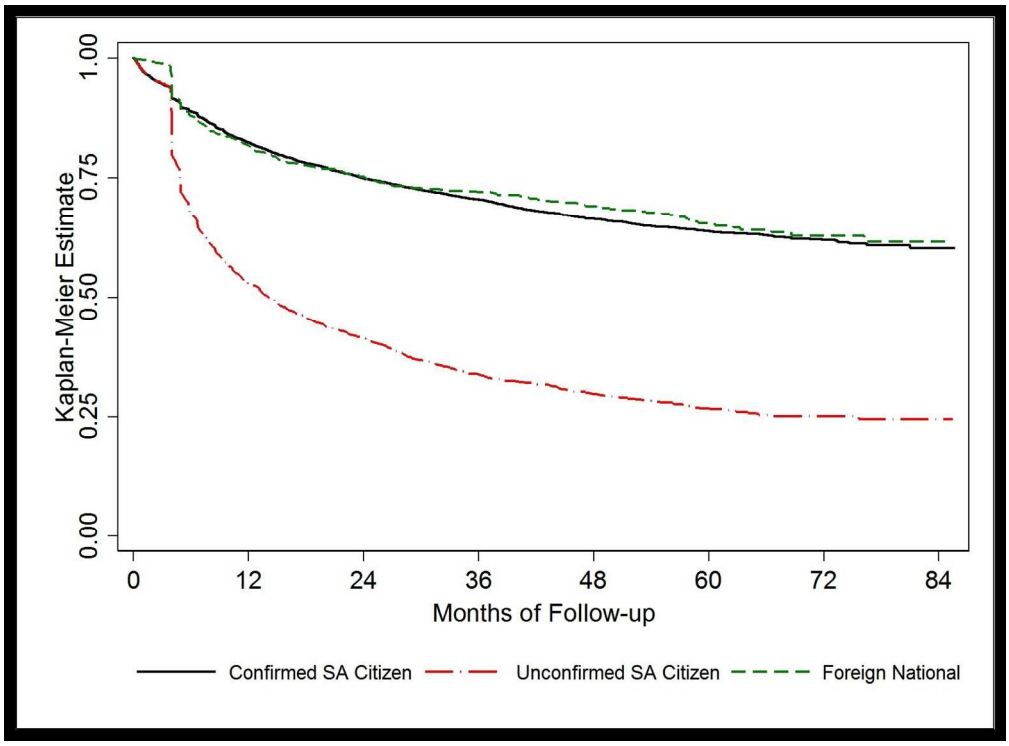

Figure 1b – Kaplan-Meier curve depicting time to death or loss to follow-up ever after ART initiation among patients who initiated antiretroviral therapy between January 2008 and December 2013, stratified by SA citizenship status

142x104mm (300 x 300 DPI)

Appendix - Unadjusted and adjusted estimates of attrition (death and loss to follow-up) at one-year and ever after ART initiation among 12,219 patients who initiated antiretroviral therapy between January 2008 and December 2013 at the Themba Lethu Clinic in Johannesburg, South Africa

Characteristic	One-year after ART initiation		Ever after ART initiation	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Citizenship status				
Confirmed South African citizen	**Reference**	**Reference**	**Reference**	**Reference**
Unconfirmed South African citizen	3.15 (2.90, 3.41)	2.72 (2.51, 2.95)	2.99 (2.80, 3.19)	2.70 (2.52, 2.88)
Foreign national	1.02 (0.89, 1.17)	1.09 (0.95, 1.25)	0.95 (0.85, 1.05)	0.97 (0.87, 1.08)
Year of ART initiation				
2008-09	**Reference**	--	**Reference**	**Reference**
2010-11	0.93 (0.86, 1.02)	--	0.91 (0.85, 0.97)	1.11 (1.01, 1.21)
2012-13	0.94 (0.86, 1.04)	--	0.84 (0.77, 0.91)	1.17 (1.06, 1.30)
Sex				
Male	1.51 (1.40, 1.63)	1.44 (1.32, 1.57)	1.48 (1.40, 1.57)	1.47 (1.37, 1.57)
Female	**Reference**	**Reference**	**Reference**	**Reference**
Age at ART initiation				
<30	1.07 (0.95, 1.20)	0.93 (0.83, 1.05)	1.27 (1.16, 1.39)	1.15 (1.05, 1.26)
30-34.9	0.94 (0.84, 1.05)	0.81 (0.72, 0.91)	1.10 (1.01, 1.21)	1.00 (0.92, 1.10)
35-39.9	0.98 (0.87, 1.09)	0.88 (0.78, 0.98)	0.98 (0.90, 1.08)	0.91 (0.83, 0.99)
40-44.9	0.95 (0.84, 1.07)	0.91 (0.80, 1.03)	0.95 (0.86, 1.05)	0.93 (0.84, 1.03)
≥45	**Reference**	**Reference**	**Reference**	**Reference**
Employment status				
Employed	**Reference**	**Reference**	**Reference**	**Reference**
Unemployed	1.59 (1.47, 1.71)	1.36 (1.26, 1.47)	1.55 (1.46, 1.64)	1.39 (1.30, 1.47)
Baseline CD4 count (cells/mm³)				
<50	2.89 (2.55, 3.28)	1.85 (1.61, 2.11)	2.22 (2.03, 2.44)	1.59 (1.44, 1.75)
50-99	1.93 (1.68, 2.22)	1.39 (1.20, 1.60)	1.62 (1.46, 1.79)	1.27 (1.14, 1.42)
100-199	1.37 (1.20, 1.56)	1.18 (1.03, 1.35)	1.35 (1.23, 1.49)	1.23 (1.11, 1.35)
≥200	**Reference**	**Reference**	**Reference**	**Reference**
BMI at ART initiation (kg/m²)				
<18.5	1.82 (1.64, 2.00)	1.31 (1.17, 1.45)	1.64 (1.52, 1.78)	1.27 (1.16, 1.38)
18.5-24.9	**Reference**	**Reference**	**Reference**	**Reference**
25-29.9	0.59 (0.51, 0.68)	0.79 (0.69, 0.92)	0.65 (0.59, 0.73)	0.85 (0.76, 0.95)
≥30	0.49 (0.40, 0.60)	0.75 (0.60, 0.92)	0.56 (0.49, 0.65)	0.81 (0.69, 0.94)
WHO Stage				
I/II	**Reference**	**Reference**	**Reference**	**Reference**
III/IV	1.97 (1.82, 2.12)	1.24 (1.13, 1.35)	1.67 (1.58, 1.78)	1.18 (1.10, 1.27)
Anemia at ART initiation				
No Anemia	**Reference**	**Reference**	**Reference**	**Reference**
Mild Anemia	1.40 (1.23, 1.60)	1.13 (0.98, 1.29)	1.22 (1.11, 1.33)	1.04 (0.94, 1.14)
Moderate Anemia	2.04 (1.82, 2.28)	1.53 (1.36, 1.74)	1.56 (1.43, 1.69)	1.27 (1.16, 1.39)
Severe Anemia	3.77 (3.28, 4.32)	2.36 (2.02, 2.75)	2.47 (2.22, 2.75)	1.74 (1.55, 1.96)
Co-infected with tuberculosis at ART initiation				
No	**Reference**	**Reference**	**Reference**	**Reference**
Yes	1.54 (1.39, 1.70)	0.90 (0.80, 1.00)	1.52 (1.40, 1.65)	0.99 (0.90, 1.08)
First ART regimen[λ]				

TDF-3TC-EFV	**Reference**	**Reference**	**Reference**	**Reference**
d4T-3TC-EFV	1.15 (1.06, 1.24)	0.90 (0.83, 0.98)	1.20 (1.12, 1.28)	1.06 (0.98, 1.16)
AZT-3TC-EFV	1.31 (1.05, 1.65)	1.19 (0.94, 1.50)	1.22 (1.01, 1.48)	1.15 (0.95, 1.41)
Other	0.80 (0.70, 0.92)	0.91 (0.79, 1.04)	0.94 (0.85, 1.05)	1.02 (0.91, 1.14)

[λ]TDF=Tenofovir; 3TC=lamivudine; EFV=efavirenz; d4T=stavudine; AZT=zidovudine; Other regimens are: TDF-3TC-NVP (nevirapine), AZT-3TC-NVP, TDF-EMT (emtricitabine)-EFV, TDF-EMT-NVP, and d4T-3TC-NVP

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6-7
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, explain how loss to follow-up was addressed	6
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	7
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7-8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.