BMJ Open

Antiretroviral therapy uptake and predictors of virological failure in patients with HIV receiving first-line and second-line regimens in Johannesburg, South Africa: a retrospective cohort data analysis

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To cite: Gumede SB, Venter F, de Wit J, *et al*. Antiretroviral therapy uptake and predictors of virological failure in patients with HIV receiving first-line and second-line regimens in Johannesburg, South Africa: a retrospective cohort data analysis. *BMJ Open* 2022;**12**:e054019. doi:10.1136/bmjopen-2021-054019

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-054019).

Received 31 May 2021
Accepted 23 March 2022

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ABSTRACT

Objective This study described the demographics, treatment information and identified characteristics associated with virological failure and being lost to follow-up (LTFU) for patients with HIV on first-line and second-line antiretroviral therapy (ART) regimens in a large South African cohort.

Design A quantitative retrospective cohort study using secondary data analysis.

Setting Seven Johannesburg inner city facilities.

Participants Unique records of 123 002 people with HIV receiving ART at any point in the period 1 April 2004 to 29 February 2020 were included.

Measures Demographic characteristics, ART status, CD4 count information and retention status were collected and analysed as covariates of outcomes (viral load (VL) and LTFU).

Results Of the total study patients, 95% (n=1 17 260) were on a first-line regimen and 5% (n=5742) were on a second-line regimen. Almost two-thirds were female (64%, n=79 226). Most patients (60%, n=72 430) were initiated on an efavirenz-based, tenofovir disoproxil fumarate-based and emtricitabine-based regimen (fixed-dose combination). 91% (n=76 737) achieved viral suppression at least once since initiating on ART and 60% (n=57 981) remained in care as at the end of February 2020. Patients from the community health centre and primary healthcare clinics were not only more likely to be virally suppressed but also more likely to be LTFU. Patients on second-line regimens were less likely to reach viral suppression (adjusted OR (aOR)=0.26, CI=0.23 to 0.28) and more likely to be LTFU (aOR=1.21, CI=1.09 to 1.35). Being older (≥25 years) and having a recent CD4 cell count≥100 cells/µL were predictors of viral suppression and retention in patients on ART.

Conclusion Patients on first-line regimens had higher VL suppression rates and were more likely to remain in care than those on a second-line regimen. Being younger and having low CD4 cell counts were associated with poor outcomes, suggesting priority groups for ART adherence support.

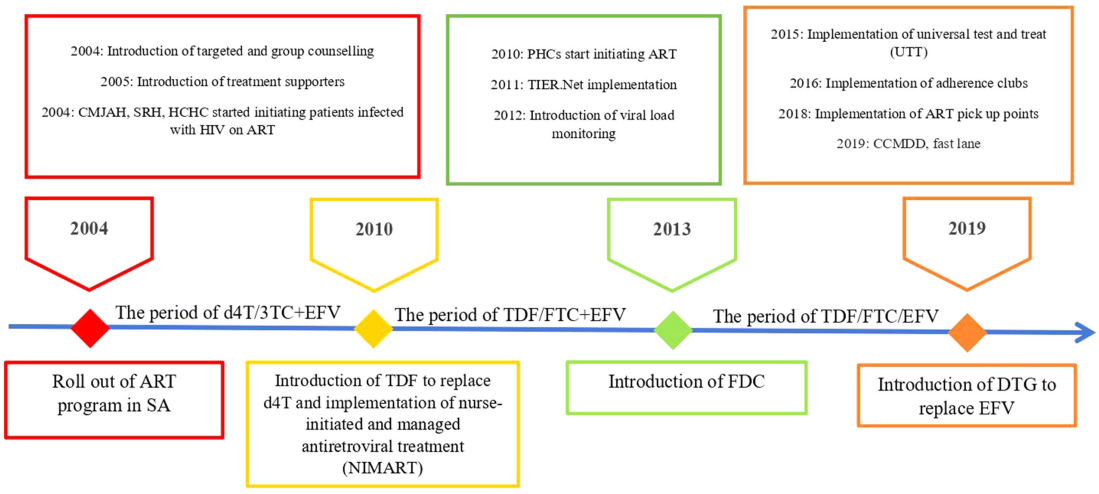
Strengths and limitations of this study

- ► This is one of the largest studies to date from the South African national HIV treatment programme reporting on antiretroviral therapy uptake, virologic failure and retention in care.
- ► Data are presented from 2004, the inception of the national HIV treatment programme in the public health system setting.
- ► The study identified groups for prioritising interventions to improve clinical and retention outcomes.
- ► The analyses were completed for only 7 of over 120 health facilities in one South African metropolitan municipality.
- ► Due to data inconsistencies, we could not accurately calculate time to viral load suppression or failure.

INTRODUCTION

Antiretroviral therapy (ART) is critical to maintain HIV viral load (VL) suppression, improve immunologic function and reduce HIV-related morbidity and mortality.[1 2] Therefore, provision of ART to people with HIV has continued to be scaled up, with an estimated 24.5 million people with HIV taking ART globally in 2019.[3 4] South Africa contributes about 20% (4.8 million) of the global number of HIV-positive people accessing ART.[5 6]

Many countries, including South Africa, follow the WHO recommendations for first-line and subsequent-line ART.[2 7] South Africa replaced stavudine (d4T) with tenofovir disoproxil fumarate (TDF) in 2010 and is transitioning from efavirenz (EFV)-based first-line treatments and protease inhibitor (PI)-based second-line treatments to dolutegravir (DTG)-based regimens (figure 1); all



Period (years)	CD4 cell count threshold	Average baseline CD4 cell count (at ART initiation) for the study cohort
2004-2010	≤200 cells/ mm3	156 cells/ mm3
2011-2014	≤350 cells/mm3	209 cells/ mm3
2015	≤500 cells/ mm3	284 cells/ mm3
2016-To date	No CD4 cell count threshold	331 cells/ mm3

Figure 1 Evolution of ART and changes in CD4 cell count thresholds in South Africa. ART, antiretroviral therapy; d4T, stavudine; DTG, dolutegravir; EFV, efavirenz; FDC, fixed-dose combination of TDF/FTC//EFV; FTC, emtricitabine; PHCs, primary healthcare clinics; SA, South Africa; 3TC, lamivudine; TDF, tenofovir disoproxil fumarate.

regimens include emtricitabine (FTC) or lamivudine (3TC).[7–9]

In 2019, an estimated 15%–20% of people on first-line ART and up to 30% of people on second-line ART in the South African HIV treatment programme experienced virological failure.[10–13] Further, up to approximately 40% of people on first-line ART and up to 20% of people with HIV on second-line ART were lost to-follow-up (LTFU), defined as patients who missed their clinic appointment by over 90 days or did not collect their ART without being confirmed as having died or transferred out.[10–14] Identifying factors which predict high risk of treatment failure and/or non-retention in care on either first-line or second-line ART will facilitate the development of mitigation interventions in these groups.

This study describes the overall demographics and treatment information of a large cohort initiating first-line and second-line ART regimens in central Johannesburg. It further identifies demographic and clinical characteristics that predict virological failure and LTFU.

METHODS

Study design

TIER.Net is the ART patient and data management system for the digitisation of paper registers that was developed by the University of Cape Town Centre for Infectious Disease Epidemiology and Research, in collaboration with the South African National Department of Health (SA NDoH).[15 16] TIER.Net allows public health facilities to record and monitor patients on ART and tuberculosis treatment across the continuum of care.[15 16] The system commenced roll out in 2011 and full functionality/sign off required all records to be back captured so that the system could then be used prospectively. To account for files that may have been misplaced, data were also captured from the ART longitudinal paper-based registers—in use at all public health facilities prior to the TIER.Net electronic version being implemented. The information retrieved from the ART longitudinal paper-based register included patient folder or unique number, sex, ART start date, CD4 at baseline, ART regimen at baseline, duration on ART, retention status, date of ART switch and current ART regimen. Time taken for facilities to be signed off was dependent on the resources available to capture and clean the data. Data quality was completed using standard operating procedures provided by the SA NDoH. This was a quantitative retrospective cohort study using secondary analysis of data on people with HIV taking ART (18 years and older) recorded in the TIER.Net database and an expansion of a study conducted on patients receiving second-line ART in the Johannesburg inner city (region F).[10]

Setting

Seven high volume public health facilities that were operational at the time of data extraction and had a functional TIER.Net system in the Johannesburg inner city (subdistrict F) were included in the study. This included two hospitals, one community health centre (CHC) and four primary healthcare clinics (PHCs).

Brief description and frequency of ART visits

All health facilities provide ART services as per WHO and South African ART guidelines.[2 17] Following an HIV diagnosis, a package of HIV and ART care services is offered

to ensure timely linkage to care. This includes adherence counselling, clinical assessment (monitoring of VL, CD4 cell count and creatine), ART initiation and any psychosocial support if needed. Importantly, clinic visits are different for each patient in terms of clinical monitoring, ART medication and adherence support offered. For stable or virally suppressed patients, clinic visits can be scheduled between 3 and 6 months in line with WHO recommendations.[17] As part of differentiated care patients may attend adherence clubs or receive ART outside of conventional health facilities and these visits are likely to occur semiannually. Patients who have an unsuppressed HIV VL mainly attend monthly clinic visits and have their VL monitored more frequently (VL repeated in 2 months following the first unsuppressed VL reading).[2 17] In most cases, patients are provided with sufficient ART to last for the period between clinic visits (exceptions linked to medication shortages in which the patient will return to the facility only for a medication collection and not wait in line for a clinical consultation). Patients who are unable to attend their next appointment are encouraged to communicate with health facilities to reschedule within the first 3 months of the missed appointment. With the current systems and non-linked TIER.Net, it is difficult to control patients who leave one health facility to another without appropriate or official transfer-out information (these patients are regarded as self-transfer-out patients). Self-transfer-out negatively affects LTFU rates as most of these patients are active in another facility while regarded as LTFU in their original health facility.

Record selection and data extraction

Study data were extracted in March 2020. Records of people with HIV who started ART between 1 April 2004 (the inception of the South African national HIV treatment programme in the public health system setting) and 29 February 2020 from the seven public health facilities were included in the study.

Overall, 233 593 records were available in the TIER.Net database. Records were excluded as follows: 104 757 records of patients who were not on ART; 406 records of patients who were initiated prior to April 2004; 3739 records of patients who were younger than 18 years; 1628 records of patients on third-line ART and 51 records of patients with inaccurate regimen information captured. Overall, 123 002 records of people with HIV taking ART (first-line regimen and second-line regimen) were included (figure 2).

TIER.Net data were exported to Microsoft Excel 2016 Professional Plus. Extracted variables included: treatment facility, sex, patient's age at ART start, patient's current age, ART start date, baseline ART regimen, last prescribed ART regimen, CD4 cell count at start of ART, most recent CD4 cell count (the last recorded CD4 cell count result), most recent VL count (the last recorded VL result) and retention in care status.

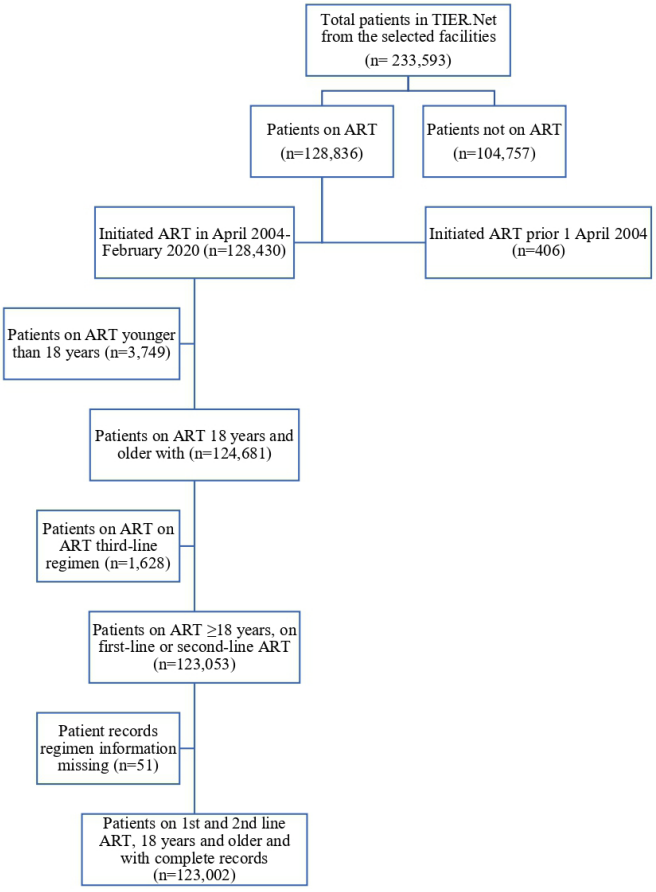


Figure 2 Flow diagram for the selection of study records. ART, antiretroviral therapy. Note: Patients not on ART include (1) patients who did not qualify to commence ART because of guideline mandated CD4 cell count thresholds (prior to the test and treat strategy); (2) decision not to start ART made by a clinician and (3) patients who did not complete pre treatment procedures, such as counselling.

The recoding of continuous variables, such as CD4 cell count and VL count, into categorical variables was informed by WHO guidelines and thresholds.[17–21] The CD4 cell count values were categorised into the following ranges: <100 cells/µL, 101–200 cells/µL, 201–350 cells/µL, 351–500 cells/µL and above 500 cells/µL.[17–19]

Outcomes

VL count was categorised into suppressed (<1000 copies/mL) or unsuppressed (≥1000 copies/mL).[20 21] Virological failure, according to the WHO, is defined as two consecutive VLs≥1000 HIV RNA copies/mL repeated within 2 months.[22] The status on retention in care for patients was categorised into active in care, LTFU, transferred out or recorded dead. For this study, LTFU was defined as having missed a scheduled medical appointment by 90 days or more, as defined by the SA NDoH. Unrecorded LTFU, transfer out and deaths were all recorded as LTFU as defined by the SA NDoH.[14]

Data analysis

Data were analysed using Stata V.15.1 (StataCorp, USA). Continuous demographic data were summarised and

analysed using median and IQR statistics, where appropriate, and then grouped into categories. Transfers out were excluded in the calculation of retention rates, since these patients were not expected to be in care in the included facilities, however deaths and LTFU were included.[14 23 24] Pearson χ^2 tests were used to assess associations between outcome variables (VL and retention in care status) and demographic characteristics (age at start of ART, current age, sex, health facility). Univariate and multivariable logistic regression models of the outcome variables were constructed to control for confounders and identify independent predictors. We also fitted multivariable logistic regression models with individual fixed effects. Associations with these predictors are reported as unadjusted (crude) and adjusted ORs (aORs), with 95% CIs and p values; p values smaller than 0.05 are considered statistically significant. To assess predictors of retention, survival analysis, using the Kaplan-Meier estimator, was performed for LTFU (patients who are no longer in care at the health facility and were not confirmed as transferred out or died) category.

Patient and public involvement

Patients and the public were not involved in the design and conduct of the study.

RESULTS

In total, records of 123 002 people with HIV were included (95% (n=117 260) on a first-line regimen and 5%, (n=5742) on a second-line regimen). Table 1 shows participants' characteristics by ART regimen. Almost two-thirds of patients whose records were included were women (64%, n=79 226). Patients' median age at the start of ART was 33 years (IQR 28–39 years); at the time of data extraction, patients' average age was 38 years (IQR 32–45 years). At ART start, 15% patients (n=18 476) were 25 years or younger, 6% patients (n=6945) were 50 years and above, and this latter group increased to 14% patients (n=17 323) at the time of data extraction.

The average duration on ART was 64 months (IQR 31–105 months), with patients on a first-line regimen having shorter treatment durations (62 months, 30–103 months) than those on a second-line regimen (107 months, 75–131 months). The average CD4 cell count of patients initiating ART at different points in time increased steadily, from 156 cells/µL between 2004 and 2010 to 209 cells/µL between 2011 and 2014, 284 cells/µL in 2015, 329 cells/µL between 2016 and 2018 and 336 cells/µL between 2019 and 2020. Overall, 98 626 patients had a recent CD4 cell count recorded in the TIER.Net database. Of these, 27% (n=26 997) had CD4 cell counts>500 cells/µL (16% increase from baseline CD4 cell count) at their most recent measurement, while 13% (n=12 432) had CD4 cell count≤100 cells/µL representing a 12% decrease from the baseline CD4 cell count.

At the time of the data extraction for this study, just over 1% of people with HIV receiving ART were on DTG (n=1479); 792 patients were initiated on DTG as new patients and 687 switched from EFV to DTG. Of the total cohort, 47% (n=57 981) were still active in care, with 32% (n=39 195) LTFU, 20%, (n=24 931) transferred out and less than a percent recorded as dead (0.7%, n=895). After combining the few known deaths with the LTFU (which already included unrecorded or self-transfer out), 32.6% (40 090) patients were lost from care, unreported transfers or deaths.

ART initiations and LTFU

The number of people starting ART are presented as annual totals in figure 3 and by regimen in table 2. The average annual number of ART initiations between 2004 and 2010 was 4092. There was a steady annual increase in the total number of people with HIV initiating ART between 2004 (n=840) and 2010 (n=8720), the period of d4T/3TC+EFV combination as the preferred first-line regimen. The average annual LTFU rate between 2004 and 2010 was 30%. The average annual number of ART initiations increased to 8772 patients per year between 2011 and 2013 (the period of TDF/3TC/EFV combination as a preferred first-line regimen), with an average of 35% LTFU rate in this period.

Antiretroviral drugs

Of the total patients initiated on ART between 2004 and 2020, 12% (n=15 074) were initiated on the d4T/3TC+EFV combination, 16% (n=19 105) were initiated on TDF/3TC/EFV combination and 59% (n=72 430) on FDC (TDF/FTC/EFV). Only 0.4% (n=451) were initiated on the tenofovir/lamivudine/dolutegravir regimen (TDF/3TC/DTG). Zidovudine accounted for 3% (n=3267) of regimens over the 16-year period. Ritonavir-boosted lopinavir (LPV/r) was the most used PI in this cohort with 91% (n=1257) of patients who started on a PI-based regimen being initiated on LPV/r.

Of patients with a completed VL on record (n=84 252), 91% (n=76 737) had achieved viral suppression, defined as ≤1000 copies/mL, at least once during treatment. The rate of VL suppression was 92% (n=72 451) for patients on a first-line regimen and 81% (n=4286) for patients on a second-line regimen.

Retention rates

Of all 123 002 patients on ART, 47% (n=57 981) remained in care at the initiating facility. The retention rate was 47% (n=54 898) among patients on a first-line regimen and 54% (n=3083) among patients on a second-line regimen. After removing transferred-out patients, leaving a total of 98 071 patients, the overall retention rate was 60% (59% among patients on a first-line regimen and 65% among patients on a second-line regimen). Survival analysis showed a steady decline in retention in care for both first-line and second-line regimens (figure 4). There was a higher decline in retention in care for patients on a first-line regimen from the start of ART throughout

Table 1 Distribution of demographic and clinical characteristics by ART regimen

	Total (N=1 23 002)		First-line regimen (N=1 17 260)		Second-line regimen (N=5742)	
Characteristic	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Age at ART start, years (N=1 23 002)	33	28–39	33	28–39	33	28–39
Current age*, years (N=1 23 002)	38	32–45	38	32–45	41	36–47
Duration on ART, months (N=1 23 002)	64	31–105	62	30–103	107	75–131
CD4 cell count at start of ART (N=95 697)	200 cells/µL	101–337 cells/µL	205 cells/µL	106–342 cells/µL	116 cells/µL	44–204 cells/µL
Most recent CD4 cell count* (N=98 626)	336 cells/µL	188–522 cells/µL	337 cells/µL	190–523 cells/µL	318 cells/µL	154–516 cells/µL
Viral load (N=84 252)	124 copies/mL	45–124 copies/mL	124 copies/mL	44–124 copies/mL	124 copies/mL	49–231 copies/mL
<1000 copies/mL	124 copies/mL	40–124 copies/mL	124 copies/mL	40–124 copies/mL	124 copies/mL	39–124 copies/mL
≥1000 copies/mL	36 883 copies/mL	7090–1 55 883 copies/mL	37 900 copies/mL	7225–1 59 021 copies/mL	32 271 copies/mL	6110–1 40 000 copies/mL
Characteristic	**Frequency**	**Percentage**	**Frequency**	**Percentage**	**Frequency**	**Percentage**
Facility (N=1 23 002)						
Charlotte Maxeke Hospital	11 545	9.39	10 309	8.79	1236	21.53
Hillbrow CHC	54 328	44.17	51 103	43.58	3225	56.17
Jeppe Clinic	14 765	12.00	14 647	12.49	118	2.06
Malvern Clinic	9621	7.82	9512	8.11	109	1.90
Rosettenville Clinic	8216	6.68	8138	6.94	78	1.36
South Rand Hospital	10 385	8.44	8138	8.33	613	10.68
Yeoville Clinic	14 142	11.50	13 779	11.75	363	6.32
Age at ART start, years (N=1 23 002)						
<25	18 476	15.02	17 597	15.01	879	15.31
25–34	51 649	41.99	49 287	42.03	2362	41.14
35–49	45 932	37.34	43 749	37.31	2183	38.02
50+	6945	5.65	6627	5.65	318	5.54
Current age*, years (N=1 23 002)						
<25	7875	6.40	7544	6.43	331	5.76
25–34	33 372	27.13	32 555	27.76	817	14.23
35–49	64 432	52.38	60 903	51.94	3529	61.46
50+	17 323	14.08	16 258	13.86	1065	18.55
Sex (N=1 23 000)						
Female	79 226	64.41	75 752	64.60	3474	60.50
Male	43 774	35.59	41 506	35.40	2268	39.50

Continued

Table 1 Continued

	Total (N=1 23 002)		First-line regimen (N=1 17 260)		Second-line regimen (N=5742)	
Total duration on ART, years (N=1 23 002)						
<5	48 575	39.49	47 765	40.73	810	14.11
5–9	45 791	37.23	43 691	37.26	2100	36.57
≥10	28 636	23.28	25 804	22.01	2832	49.32
Baseline CD4 cell count at start of ART (N=95 697)						
≤100 cells/µL	23 764	24.83	21 731	23.83	2033	45.00
101–200 cells/µL	24 190	25.28	22 873	25.09	1317	29.15
201–350 cells/µL	25 757	26.92	25 005	27.42	752	16.64
351–500 cells/µL	11 318	11.83	11 077	12.15	241	5.33
>500 cells/µL	10 668	11.15	10 493	11.51	175	3.87
Most recent CD4 cell count* (N=98 626)						
≤100 cells/µL	12 432	12.61	11 595	12.40	837	16.39
101–200 cells/µL	14 248	14.45	13 454	14.39	794	15.55
201–350 cells/µL	24 988	25.34	23 845	25.50	1143	22.39
351–500 cells/µL	19 961	20.24	18 984	20.30	977	19.13
>500 cells/µL	26 997	27.37	25 642	27.42	1355	26.54
Viral load (N=84 252)						
<1000 copies/mL	76 737	91.08	72 451	91.79	4286	80.61
≥1000 copies/mL	7515	8.92	6484	8.21	1031	19.39
DTG-based regimen (N=1 23 002)						
DTG-based regimen	1479	1.20	1460	1.25	19	0.33
Without DTG	121 523	98.80	115 800	98.75	5723	99.67
Retention status (N=1 23 002)						
Active in care	57 981	47.14	54 898	46.82	3083	53.69
Deceased	895	0.73	830	0.71	65	1.13
LTFU	39 195	31.87	37 588	32.06	1607	27.99
Transferred/moved out	24 931	20.27	23 944	20.42	987	17.19

*Current age=patient's age when data were extracted for the analysis from TIER.Net; most recent CD4 cell count=most recent CD4 cell count available in the database.
ART, antiretroviral therapy; DTG, dolutegravir; LTFU, lost to follow-up; N, number.

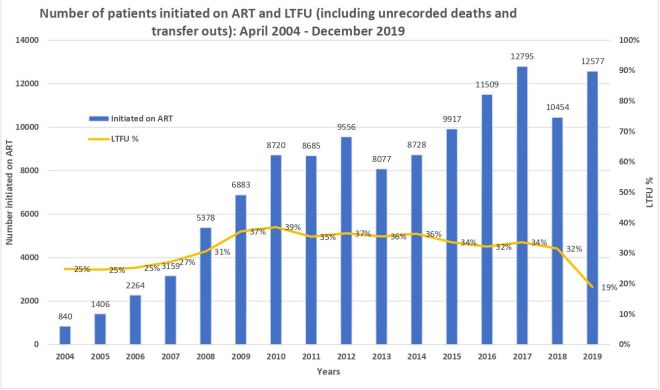


Figure 3 Numbers of ART new initiation and LTFU rate over time in the seven health facilities in subdistrict F. ART, antiretroviral therapy; LTFU, lost to follow-up. Note: LTFU rates were calculated using the proxy denominator of ART initiation in the same period. LTFU also include unaccounted for deaths and transfers. A large proportion of those LTFU are in care elsewhere or dead.

the treatment span than among those on a second-line regimen. These proportions even out after 15 years.

Factors associated with VL suppression and LTFU

Table 3 shows findings of univariate and multivariable logistic regression analyses of current ART regimen and clinical characteristics with outcome variables (VL and LTFU). VL suppression was associated with ART regimen, with patients on the second-line regimen less likely than those on a first-line regimen to achieve VL suppression (aOR=0.26, CI=0.23 to 0.28). Regimen was also a predictor of retention in care status, where patients on a second-line regimen were more likely than those receiving a first-line regimen to be LTFU (aOR=1.21, CI=1.09 to 1.35). Patients on a fixed-dose combination were more likely to be virally suppressed (aOR=1.42, CI=1.26 to 1.59) and were also less likely to be LTFU (aOR=0.017, CI=0.015 to 0.019) than those on d4T/3TC+EFV. Likewise, patients on TDF/3TC/EFV were less likely to be LTFU than patients on d4T/3TC+EFV (aOR=0.14, CI=0.12 to 0.15). Level of care was associated with VL and being LTFU, with patients from the CHC (aOR=2.20, CI=2.02 to 2.39) and PHCs (aOR=1.15, CI=1.05 to 1.25) being more likely to be virally suppressed than patients receiving ART at a hospital level. However, patients receiving ART services at the CHC (aOR=1.14, CI=1.07 to 1.21) and PHC (aOR=1.51, CI=1.42 to 1.60) levels were also more likely to be LTFU than those who receive ART at a hospital level. The fixed effects model yielded the same results and are not reported here.

First-line treatment

Table 4 shows findings of univariate and multivariable logistic regression analyses of associations of demographic and clinical characteristics with VL suppression and LTFU for patients on first-line ART (the fixed effects model yielded the same results and are not reported here). Patients aged 25–34 years (aOR=1.89, CI=1.64 to 2.17), 35–49 years (aOR=3.00, CI=2.61 to 3.44) and 50+ years (aOR=4.50, CI=3.83 to 5.29) were all more likely to attain VL suppression than patients younger than 25 years. Patients with their most recent CD4 cell count between 101–200 cells/µL (aOR=1.85, CI=1.70 to 2.02), 201–350 cells/µL (aOR=3.70, CI=3.41 to 4.01), 351–500 cells/µL (aOR=6.13, CI=5.58 to 6.74) and above 500 cells/µL (aOR=11.96, CI=10.80 to 13.24) were all more likely to have suppressed VL than patients with their most recent CD4 cell count less or equal to 100 cells/µL. Patients who were initiated on first-line ART between 2011–2014, ≤350 CD4 cell count period (aOR=1.24, CI=1.14 to 1.35), and 2015, ≤500 cell count period (aOR=1.38, CI=1.22 to 1.56), were more likely to achieve virological suppression than patients initiated between 2004 and 2010 (≤200 cells/µL period). Patients receiving first-line ART at CHC (aOR=2.67, CI=2.46 to 2.90) and PHC (aOR=1.43, CI=1.32 to 1.55) levels were more likely to achieve virological suppression than those receiving first-line ART at hospital level.

Patients aged 25–34 years (aOR=0.80, CI=0.75 to 0.86), 35–49 years (aOR=0.46, CI=0.43 to 0.49) and 50+ years (aOR=0.40, CI=0.37 to 0.43) were less likely to be LTFU than patients<25 years. Patients with a most recent CD4 cell count between 101–200 cells/µL (aOR=0.79, CI=0.75 to 0.84), 201–350 cells/µL (aOR=0.62, CI=0.60 to 0.65), 351–500 cells/µL (aOR=0.51, CI=0.49 to 0.54) and above 500 cells/µL (aOR=0.43, CI=0.41 to 0.45) were less likely to be LTFU than patients with most recent CD4 cell count≤100 cells/µL. Patients who were initiated on first-line ART between 2011 and 2014 were more likely to be LTFU as compared with those initiated prior (aOR=1.14, CI=1.09 to 1.19). Patients who were initiated on first-line ART between 2016 and 2020 were less likely to be LTFU than those initiated prior to 2011 (aOR=0.63, CI=0.60 to 0.65). Patients receiving first-line ART from CHC (aOR=1.47, CI=1.40 to 1.54) and PHC (aOR=1.56, CI=1.49 to 1.64) levels were more likely to be LTFU than those at hospital level.

Second-line treatment

Table 5 shows findings of univariate and multivariable logistic regression analyses of associations of demographic and clinical characteristics with VL suppression and LTFU for patients on second-line ART (the fixed effects model yielded the same results and are not reported here). Patients aged 25 years and older (25–34 years: aOR=2.01, CI=1.40 to 2.89, 35–49 years: aOR=3.13, CI=2.26 to 4.32 and 50+ years: aOR=3.91, CI=2.72 to 5.62) were more likely to be virally suppressed than patients younger than 25 years. Patients with recorded most recent CD4 cell counts of 101–200 cells/µL (aOR=1.28, CI=1.02 to 1.59), 201–350 cells/µL (aOR=2.19, CI=1.77 to 2.71), 351–500 cells/µL (aOR=4.13, CI=3.21 to 5.32) and above 500 cells/µL (aOR=8.32, CI=6.33 to 10.93) were more likely to achieve VL suppression than patients whose most recent CD4 cell count was ≤100 cells/µL. Patients who were initiated on second-line ART between 2011

Table 2 Number of people with HIV initiated on various antiretroviral drugs by calendar year

	≤200 cells/µL period (2004–2010)							≤350 cells/µL period (2011–2014)					Universal test and treat (CD4 cell count not required as an eligibility criteria					
CD4 cell count eligibility thresholds	Roll out of ART programme in SA						Introduction of TDF			Introduction of FDC		≤500 cells/µL period (2015)				Introduction of DTG		
	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020 (end date: 29 February)	Total
Baseline ART																		
First NRTI																		
TDF	74	136	215	416	715	871	4926	7515	8447	7537	8404	9658	11 241	12 311	10 228	12 463	2044	97 201
d4T	662	1119	1758	2296	3990	5585	3295	672	539	243	69	35	22	11	5	0	3	20 304
AZT	94	131	244	317	401	350	302	305	447	168	127	120	103	78	45	35	0	3267
ABC	4	6	4	12	18	12	79	103	101	121	121	100	139	157	152	73	7	1209
Second NRTI																		
FTC	38	57	92	207	392	266	372	679	869	5157	7984	9397	10 938	12 476	10 195	12 396	1632	73 147
3TC	786	1331	2120	2830	4723	6539	8228	7912	8658	2911	737	516	565	311	253	175	421	49 016
ddI	9	4	10	4	9	11	2	4	4	1	1	1	1	1	0	0	1	63
NNRTI																		
EFV	720	1174	1773	2313	3808	4894	6488	6810	7990	7528	8476	9745	11 384	12 244	10 276	12 489	1605	109 717
NVP	90	186	407	665	1217	1764	1943	1648	1424	428	168	104	44	39	42	11	2	10 182
InSTI																		
DTG	0	0	0	0	0	0	0	1	1	0	0	0	0	265	43	36	446	792
RAL	0	0	0	0	0	0	0	0	0	0	0	1	0	1	1	1	0	4
PIs																		
LPV/r	21	30	39	56	93	129	145	125	114	114	75	61	73	72	81	28	1	1257
ATV/r	0	0	3	1	1	1	1	0	0	0	0	2	2	12	5	6	0	34
RTV*	3	2	1	6	4	29	23	12	5	0	1	0	2	1	1	0	0	90

*There is a possibility of misreporting on TIER.Net with RTV data. Complexity of combination with ATV as well as double dosing for tuberculosis. No patient is given RTV alone if adult.
ABC, abacavir; ART, antiretroviral therapy; ATV, ritonavir-boosted atazanavir; AZT, zidovudine; ddI, didanosine; d4T, stavudine; DTG, dolutegravir; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; InSTI, integrase strand transfer inhibitor; LPV/r, ritonavir-boosted lopinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RTV, ritonavir; SA, South Africa; 3TC, lamivudine; TDF, tenofovir.

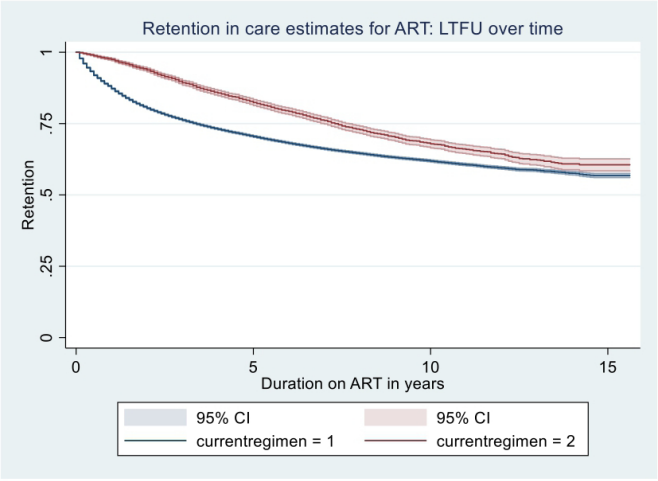


Figure 4 Survival analysis: retention over time for patients on a first-line and second-line antiretroviral therapy (ART) regimen. LTFU, lost to follow-up.

and 2014 (aOR=1.20, CI=1.01 to 1.44) were more likely to achieve virological suppression than patients initiated between 2004 and 2010. Receiving second-line ART from a PHC (aOR=0.73, CI=0.57 to 0.94) was associated with virological failure in comparison to receiving second-line ART at a hospital level. Patients who received second-line ART at a CHC level were more likely to achieve virological suppression (aOR=1.32, CI=1.11 to 1.57).

Unlike patients on first-line ART, patients on second-line ART aged 25–34 years (aOR=1.99, CI=1.36 to 2.91) and 35–49 years (aOR=1.46, CI=1.03 to 2.08) were more likely to be LTFU than patients<25 years.

Patients with a most recent CD4 cell count 201–350 cells/µL (aOR=0.70, CI=0.57 to 0.85), 351–500 cells/µL (aOR=0.70, CI=0.57 to 0.86) and 500 cells/µL (aOR=0.44, CI=0.36 to 0.54) were all less likely to be LTFU than patients with a most recent CD4 cell count≤100 cells/µL. Patients who were initiated on second-line ART between 2011–2014 (aOR=0.81, CI=0.70 to 0.93), 2015 (aOR=0.62, CI=0.46 to 0.85) and 2016–2020 (aOR=0.42, CI=0.33 to 0.52) were all less likely to be LTFU than those who were initiated between 2004 and 2010.

DISCUSSION

This is one of the largest studies to date from the South African national HIV treatment programme reporting on ART uptake, virologic failure and retention in care. In this cohort, most patients did well virologically but retention in care was poor. The outcomes observed in this study are similar to those of other studies in sub-Saharan African countries,[25–27] but different to most findings from high-income countries.[5]

Various studies have reported improved treatment outcomes and retention in care associated with FDC, also noting that the improvement extends beyond the single pill versus multi-pill ART comparison to availability of adherence support, time between medical visits

Table 3 Logistic regression analysis (univariate) for current regimen and outcome variables

Variable	VL suppression			LTFU		
	OR (95% CI)	P value	Adjusted OR (aOR)	P value	OR (95% CI)	P value	aOR	P value
Current regimen								
First-line regimen	1	–	1	–	1	–	1	–
Second-line regimen	0.37 (0.35 to 0.40)	**<0.001**	0.26 (0.23–0.28)	**<0.001**	0.82 (0.78 to 0.87)	**<0.001**	1.21 (1.09–1.35)	**<0.001**
Regimen combination								
d4t/3TC+EFV	1	–	1		1	–	1	–
TDF/3TC/EFV	1.06 (0.97 to 1.16)	0.220	1.24 (1.10–1.40)	0.797	1.14 (1.09 to 1.19)	**<0.001**	0.14 (0.12–0.15)	**<0.001**
TDF/FTC/EFV (FDC)	0.83 (0.77 to 0.90)	**<0.001**	1.42 (1.26–1.59)	**<0.001**	0.83 (0.80 to 0.86)	**<0.001**	0.017 (0.015–0.019)	**<0.001**
Level of care								
Hospital	1	–	1		1	–	1	–
CHC	1.91 (1.79 to 2.04)	**<0.001**	2.20 (2.02–2.39)	**<0.001**	1.27 (1.22 to 1.31)	**<0.001**	1.14 (1.07–1.21)	**<0.001**
PHC	1.22 (1.14 to 1.30)	**<0.001**	1.15 (1.05–1.25)	**0.001**	1.20 (1.16 to 1.25)	**<0.001**	1.51 (1.42–1.60)	**<0.001**

Bold p values denote statistical significance at the p≤0.05 level. Analysis adjusted for: CD4 at baseline or CD4 at ART initiation and duration on ART.
ART, antiretroviral therapy; CHC, community health centre; d4T, stavudine; EFV, efavirenz; FDC, fixed-dose combination; FTC, emtricitabine; LTFU, lost to follow-up; PHC, primary healthcare clinic; 3TC, lamivudine; TDF, tenofovir; VL, viral load.

Table 4 Logistic regression analysis (univariate and multivariable analysis) for patients on first-line ART regimens

	VL suppression				LTFU			
Variable	**OR (95% CI)**	**P value**	**Adjusted OR (aOR) (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**aOR (95% CI)**	**P value**
Current age (years)								
<25	1	–	1	–	1	–	1	–
25–34	1.54 (1.40 to 1.71)	**<0.001**	1.89 (1.64 to 2.17)	**<0.001**	0.97 (0.92 to 1.01)	0.196	0.80 (0.75 to 0.86)	**<0.001**
35–49	2.25 (2.05 to 2.48)	**<0.001**	3.00 (2.61 to 3.44)	**<0.001**	0.71 (0.67 to 0.74)	**<0.001**	0.46 (0.43 to 0.49)	**<0.001**
50+	3.43 (3.05 to 3.87)	**<0.001**	4.50 (3.83 to 5.29)	**<0.001**	0.63 (0.59 to 0.66)	**<0.001**	0.40 (0.37 to 0.43)	**<0.001**
Sex								
Female	1	–	1	–	1	–	1	–
Male	0.91 (0.87 to 0.96)	**0.001**	1.06 (0.99 to 1.12)	0.082	1.01 (0.98 to 1.04)	0.478	1.03 (1.00 to 1.06)	0.061
Most recent CD4 cell count								
≤100 cells/µL	1	–	1	–	1	–	1	–
101–200 cells/µL	1.88 (1.73 to 2.04)	**<0.001**	1.85 (1.70 to 2.02)	**<0.001**	0.81 (0.77 to 0.85)	**<0.001**	0.79 (0.75 to 0.84)	**<0.001**
201–350 cells/µL	3.68 (3.39 to 3.98)	**<0.001**	3.70 (3.41 to 4.01)	**<0.001**	0.67 (0.64 to 0.70)	**<0.001**	0.62 (0.60 to 0.65)	**<0.001**
351–500 cells/µL	5.81 (5.30 to 6.38)	**<0.001**	6.13 (5.58 to 6.74)	**<0.001**	0.54 (0.51 to 0.57)	**<0.001**	0.51 (0.49 to 0.54)	**<0.001**
>500 cells/µL	10.33 (9.36 to 11.40)	**<0.001**	11.96 (10.80 to 13.24)	**<0.001**	0.46 (0.44 to 0.49)	**<0.001**	0.43 (0.41 to 0.45)	**<0.001**
Years of ART initiation								
2004–2010 (≤200 cells/µL period)	1	–	1	–	1		1	–
2011–2014 (≤350 cells/µL period)	0.93 (0.86 to 1.00)	0.053	1.24 (1.14 to 1.35)	**<0.001**	1.13 (1.09 to 1.17)	**<0.001**	1.14 (1.09 to 1.19)	**<0.001**
2015 (≤500 cells/µL period)	0.94 (0.84 to 1.05)	0.257	1.38 (1.22 to 1.56)	**<0.001**	1.01 (0.96 to 1.06)	0.645	0.97 (0.92 to 1.03)	0.304
2016–2020 (universal test and treat period)	0.61 (0.57 to 0.65)	**<0.001**	0.93 (0.85 to 1.01)	0.098	0.76 (0.74 to 0.79)	**<0.001**	0.63 (0.60 to 0.65)	**<0.001**
Level of care								
Hospital	1		1		1		1	
CHC	1.99 (1.85 to 2.14)	**<0.001**	2.67 (2.46 to 2.90)	**<0.001**	1.30 (1.25 to 1.35)	**<0.001**	1.47 (1.40 to 1.54)	**<0.001**
PHC	1.13 (1.05 to 1.21)	**0.001**	1.43 (1.32 to 1.55)	**<0.001**	1.22 (1.18 to 1.26)	**<0.001**	1.56 (1.49 to 1.64)	**<0.001**

Bold p values denote statistical significance at the p≤0.05 level.
ART, antiretroviral therapy; CHC, community health centre; LTFU, lost to follow-up; PHC, primary healthcare clinic; VL, viral load.

Table 5 Logistic regression analysis (univariate and multivariable analysis) for patients on second-line ART regimens

	VL suppression				LTFU			
Variable	**OR (95% CI)**	**P value**	**Adjusted OR (aOR) (95% CI)**	**P value**	**OR (95% CI)**	**P value**	**aOR (95% CI)**	**P value**
Current age (years)								
<25	1	–	1	–	1	–	1	–
25–34	1.72 (1.30 to 2.29)	**<0.001**	2.01 (1.40 to 2.89)	**<0.001**	1.57 (1.17 to 2.10)	**0.003**	1.99 (1.36 to 2.91)	**<0.001**
35–49	2.73 (2.13 to 3.50)	**<0.001**	3.13 (2.26 to 4.32)	**<0.001**	1.30 (1.00 to 1.69)	0.054	1.46 (1.03 to 2.08)	**0.034**
50+	3.52 (2.63 to 4.70)	**<0.001**	3.91 (2.72 to 5.62)	**<0.001**	1.02 (0.76 to 1.36)	0.888	1.09 (0.75 to 1.58)	0.658
Sex								
Female	1	–	1	–	1	–	1	–
Male	0.90 (0.78 to 1.03)	0.135	1.05 (0.89 to 1.23)	0.568	0.87 (0.78 to 0.99)	**0.027**	0.89 (0.78 to 1.01)	0.077
Most recent CD4 cell count								
≤100 cells/µL	1	–	1	–	1	–	1	–
101–200 cells/µL	1.37 (1.10 to 1.70)	**0.004**	1.28 (1.02 to 1.59)	**0.031**	1.01 (0.82 to 1.24)	0.923	0.95 (0.77 to 1.18)	0.663
201–350 cells/µL	2.27 (1.85 to 2.80)	**<0.001**	2.19 (1.77 to 2.71)	**<0.001**	0.78 (0.64 to 0.94)	**0.011**	0.70 (0.57 to 0.85)	**<0.001**
351–500 cells/µL	4.17 (3.27 to 5.33)	**<0.001**	4.13 (3.21 to 5.32)	**<0.001**	0.82 (0.67 to 1.01)	0.059	0.70 (0.57 to 0.86)	**0.001**
>500 cells/µL	8.23 (6.33 to 10.71)	**<0.001**	8.32 (6.33 to 10.93)	**<0.001**	0.53 (0.44 to 0.64)	**<0.001**	0.44 (0.36 to 0.54)	**<0.001**
Years of ART initiation								
2004–2010 (≤200 cells/µL period)	1	–		–	1		1	–
2011–2014 (≤350 cells/µL period)	0.89 (0.76 to 1.04)	0.148	1.20 (1.01 to 1.44)	**0.040**	0.90 (0.79 to 1.03)	**0.126**	0.81 (0.70 to 0.93)	**0.004**
2015 (≤500 cells/µL period)	0.79 (0.58 to 1.07)	0.127	1.21 (0.86 to 1.70)	**0.285**	0.71 (0.54 to 0.95)	**0.019**	0.62 (0.46 to 0.85)	**0.003**
2016–2020 (universal test and treat period)	0.73 (0.60 to 0.89)	**0.002**	1.14 (0.90 to 1.44)	**0.284**	0.52 (043 to 0.63)	**<0.001**	0.42 (0.33 to 0.52)	**<0.001**
Level of care								
Hospital	1				1		1	
CHC	1.18 (1.01 to 1.37)	**<0.001**	1.32 (1.11 to 1.57)	**<0.001**	0.88 (0.78 to 1.00)	0.054	0.87 (0.69 to 1.08)	0.206
PHC	0.67 (0.54 to 0.84)	**<0.001**	0.73 (0.57 to 0.94)	**0.014**	0.80 (0.66 to 0.99)	**0.035**	0.90 (0.78 to 1.04)	0.153

Bold p values denote statistical significance at the p≤0.05 level.
ART, antiretroviral therapy; CHC, community health centre; LTFU, lost to follow-up; PHC, primary healthcare clinic; VL, viral load.

and patient waiting times.[28 29] In our analyses, patients on FDC were similarly more likely to achieve virological suppression and less likely to be LTFU. The simultaneous introduction of FDC and improvements in adherence interventions may have facilitated the improvement treatment outcomes and decline of LTFU between 2013 and 2019.[29]

Since the substitution of EFV with DTG, as of September 2019, less than 1500 patients were either initiated or switched to a DTG containing regimen by the end of February 2020. This accounted for 1% of the study cohort who were initiated or switched to DTG-based regimen in less than 6 months (between September 2019 and February 2020). The transition to a DTG-based regimen in South Africa is being done in a phased approach, and numbers of patients initiating DTG are expected to increase in subsequent years. Although the efficacy of DTG has been documented through clinical trials,[30 31] the clinical benefits in this population are yet to be reported.

There was a correlation between level of care (facility type) and outcome variables (VL and LTFU). Expectedly, patients receiving ART services from the CHC and PHCs were more likely to achieve virological suppression but were also more likely to be LTFU than patients receiving ART services from the hospital level. Patients with HIV-related complications and other comorbidities are likely to have poorer outcomes[32 33] and are more often likely to receive ART services at hospital level.[33] Therefore, differences in outcomes between facilities (CHC and PHCs vs hospitals) may be partially attributable to these confounders. Additionally, favourable outcome in terms of virological suppression at PHC level when compared with hospitals could also be a demonstration of effective task shifting and decentralisation of services between primary and higher levels of care (secondary and tertiary) as well as out of the facility setting (eg, PHCs and CHCs run adherence clubs for stable, adherent ART patients).[10] These levels of care could be used to provide models to improve virological suppression and adherence to treatment for hospitals as well.

With respect to first-line regimens, patients who were 25 years and older, patients with a most recent CD4 cell count above 100 cells/µL and patients who were initiated from 2011 onwards were all more likely to achieve VL suppression and remain in care. Since 2011, the South African ART programme has seen improvements in ART regimens (eg, changes from triple therapy to FDC in 2013) and CD4 cell count thresholds (eg, changes from 350 to 500 cells/µL in 2015) which has most likely attributed to better clinical outcomes.[2] These findings are consistent with the other studies which reported older patients who had higher CD4 cell counts and/or initiated from 2011 onwards being more likely to obtain VL suppression and also remain in care.[25–27 34–36] Therefore, patients under 25 years, patients with a low CD4 cell count and those who were initiated between 2004 and 2010 need to be prioritised for interventions addressing treatment and adherence. Younger patients and low CD4 cell count have been previously noted for targeting in HIV treatment programme strengthening,[25–27 34–36] and our analyses reinforces that these population groups remain at higher risk of less favourable treatment outcomes.

For patients on second-line regimens, higher CD4 cell count and patients who were initiated in 2011 onwards also predicted viral suppression and retention in care, as among patients on first-line treatment. However, being older predicted poor retention in care for patients on second-line ART, a finding that is inconsistent with previous findings from the same setting.[10] Furthermore, and similar to patients on first-line treatment, patients on second-line ART who were initiated from 2011 onwards were less likely to be LTFU. These findings corroborate other studies conducted in South Africa,[28 29] and emphasise the importance of continuous improvement in ART service delivery, including implementation of appropriate adherence support mechanisms for medication and clinic visits and optimised treatment regimens.

Survival analysis demonstrated an immediate sharp decrease in retention in care for patients on first-line ART and started plateauing at year 5, while for patients on second-line ART, retention decreased steadily with increased time on ART. Early after ART initiation there are more transfers out, deaths and loss from care than at the point of switch to second-line, however after 15 years the proportions even out. Furthermore, decrease in retention in 2007–2011 period corresponds to a time of increasing ART decentralisation. Our finding suggests a need to engage patients throughout their treatment journey by possibly providing regular adherence counselling and community-based interventions such as adherence clubs.[37 38] These treatment adherence strategies have already been noted to yield good retention and clinical outcomes in many first-line ART cohorts in lower-middle-income countries.[39 40]

VL suppression reduces the risk of HIV onward transmission and indicates good clinical outcomes and treatment adherence.[10 41 42] Overall, the high rates (91%) of VL suppression found in our study cohort is in keeping with the 90–90–90 UNAIDS targets, which includes making sure that 90% of all patients taking ART have suppressed VLs.[43 44] This suggests that prioritising interventions to promote adherence and VL monitoring in patients receiving ART has likely resulted in VL improvements. In contrast, we report higher LTFU up rates (32%) for the entire study cohort than previously reported in the Johannesburg inner city (region F) (between 10% and 20%).[10 29] A study conducted in South Africa reported approximately up to 40% being LTFU within the first year of starting ART.[45] With the current recording systems, true LTFU cannot be measured and until South Africa employs a unique identifier system, the HIV programme will not be able to accurately report on people lost to the programme as opposed to stopping treatment at one facility and starting at another (without following the transfer processes).

Overall, findings regarding predictors of VL and LTFU for both regimens underscore the need to strengthen, possibly combined, strategies to not only promote adherence to ART but also to ensure that patients are retained in HIV care.[10 37] Effective strategies to improve adherence among patients on ART comprise intensive and targeted adherence counselling and sending treatment reminders.[10 37 45] Recommendations from patients attending ART clinics in the Johannesburg inner city (region F) include reducing the pill size, education on the benefits of taking ART and making injectable ART available.[46 47] As the duration between clinic visits can span up to 6 months, it is also crucial to consider approaches to enable continued patient-provider engagement between these visits to promote retention, for instance, regular provision of health gamification and videos/health resources using mHealth platforms.[48 49]

Our study has some limitations. The analyses were completed for only 7 of over 120 health facilities in one South African metropolitan municipality, and findings may not be generalisable to other municipalities and districts in South Africa or to other country settings. Furthermore, although the department of health tries to ensure good quality of data in Tier.Net, we did encounter quality issues. In particular, due to data inconsistencies and missing information (TIER.Net only records the most recent VL count which overrides the previously captured value), we could not accurately calculate time to VL suppression or failure with only one VL reading available. A standard VL result of 124 copies/mL is captured in TIER.Net for patients whose laboratory results are reported as lower than detectable level. This makes it difficult to differentiate between patients who had an absolute value of VL results as '124' and those who had VL results as 'lower than detectable level'. This affects the calculated VL values such as the exact average VL count for the cohort. TIER.Net does not enable linking records between health facilities which results in a lack of documentation of a large proportion of transfers. It is plausible that this limitation in data increased during the 16-year study window as more facilities offering ART services became available for patients to transfer between. Deaths and LTFU are poorly recorded on TIER.Net, therefore, it is possible that death and LTFU rates are generally higher than reported in this study. While the LTFU has increased and a lot of patients who missed their appointments were regarded as LTFU after 90 days without medication, it is possible that some of these patients regarded as LTFU are in fact receiving healthcare services at other facilities (self-transfer out).[5] The association between lower CD4 count and increased LTFU could possibly be explained as the lower CD4 count (and accompanying poor health) resulted in unrecorded deaths subsequently contributing to the increased LTFU. Lastly, filing systems for paper-based records in many public health facilities in the study setting are inadequate. Therefore, it is possible that some files were misplaced or not available for back capture. However, to maximise the captured records, information was captured from patient files and the ART longitudinal paper-based register which was used in the public health setting before the TIER.Net electronic version was implemented.

CONCLUSION

While national ART guidelines and efforts to initiate people with HIV on treatment have contributed to a higher uptake of ART over time, much still needs to be done to improve retention in care; mostly in patients on a first-line regimen, and clinical outcomes; mostly in patients on a second-line regimen. Younger patients, patients with low CD4 cell counts and patients who were initiated on ART between 2004 and 2010 all showed poorer clinical and retention outcomes. Although slight efforts have been made to address similar findings, these demographic and clinical characteristics must be considered when designing/implementing treatment support strategies and models to improve retention in care. Support strategies could include directed patient management from the commencement of ART, community-based interventions, such as adherence clubs and ART pick-up points, or using digital health technology innovations for patient engagement between clinic visits, appointment and medication reminders and education.

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Acknowledgements The authors would like to thank all the facilities and relevant health and research authorities from the city of Johannesburg for allowing the research team to engage in a partnership to strengthen health service delivery through technical assistance and research.

Contributors Designed the study and interpreted the results: SBG; data extraction and analysis and wrote the initial draft: SBG and STL-E; contributed to subsequent drafts and critically reviewed and approved the final version: all authors. SBG and STL-E were the guarantors of this work and had full access to all the data in the study and took responsibility for the accuracy of the data analysis and integrity for the overall content.

Funding This study was funded by the Department of Interdisciplinary Social Science at Utrecht University (no award/grant number received) as part of the joint doctorate programme between Utrecht University and University of the Witwatersrand. SBG was supported by the Consortium for Advanced Research Training in Africa (CARTA). CARTA is jointly led by the African Population and Health Research Center and the University of the Witwatersrand and funded by the Carnegie Corporation of New York (Grant No—G-19-57145), Sida (Grant No:54100113), Uppsala Monitoring Centre and the DELTAS Africa Initiative (Grant No: 107768/Z/15/Z). The DELTAS Africa Initiative is an independent funding scheme of the African Academy of Sciences (AAS)'s Alliance for Accelerating Excellence in Science in Africa (AESA) and supported by the New Partnership for Africa's Development Planning and Coordinating Agency (NEPAD Agency) with funding from the Wellcome Trust (UK) and the UK government. The statements made and views expressed are solely the responsibility of the Fellow. Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number UG3HL156388. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval We obtained ethical clearance from the University of the Witwatersrand Human Research Ethics Committee (M190641). Departmental approval was granted by the Johannesburg Health District (DRC Ref: 2019-10-005; National Health Research Database reference number: GP_201910_031). There was neither interaction with the patients nor access to their individual medical records. An anonymized data extract was used for the analyses.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

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REFERENCES

1 World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV - Interim guidance, 2018. Available: https://www.who.int/publications/i/item/WHO-CDS-HIV-18.51 [Accessed 17 Aug 2020].
2 Meintjes G, Moorhouse MA, Carmona S, *et al*. Adult antiretroviral therapy guidelines 2017. *South Afr J HIV Med* 2017;18:776.
3 World Health Organization. HIV/AIDS: key facts, 2019. Available: https://www.who.int/news-room/fact-sheets/detail/hiv-aids. https://www.who.int/news-room/fact-sheets/detail/hiv-aids [Accessed 17 Aug 2020].
4 UNAIDS. Fact sheet – world AIDS day 2019, 2019. Available: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf [Accessed 17 Aug 2020].
5 UNAIDS. UNAIDS data 2019, 2019. Available: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf [Accessed 17 Aug 2020].
6 UNAIDS. Unaids data 2019-South Africa, 2019. Joint United nations programme on HIV/AIDS. Available: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf [Accessed 22 Nov 2021].
7 World Health Organization. Update of recommendations on first-and second-line antiretroviral regimens, 2019. Available: https://apps.who.int/iris/bitstream/handle/10665/325892/WHO-CDS-HIV-19.15-eng.pdf [Accessed 17 Aug 2020].
8 Llibre JM, Pulido F, García F, *et al*. Genetic barrier to resistance for dolutegravir. *AIDS Rev* 2015;17:56–64.
9 Cottrell ML, Hadzic T, Kashuba ADM. Clinical pharmacokinetic, pharmacodynamic and drug-interaction profile of the integrase inhibitor dolutegravir. *Clin Pharmacokinet* 2013;52:981–94.
10 Gumede SB, Fischer A, Venter WDF, *et al*. Descriptive analysis of World health Organization-recommended second-line antiretroviral treatment: a retrospective cohort data analysis. *S Afr Med J* 2019;109:919–26.
11 Hermans LE, Carmona S, Nijhuis M, *et al*. Virological suppression and clinical management in response to viremia in South African HIV treatment program: a multicenter cohort study. *PLoS Med* 2020;17:e1003037.
12 Hirasen K, Fox MP, Hendrickson CJ, *et al*. Hiv treatment outcomes among patients initiated on antiretroviral therapy pre and post-universal test and treat guidelines in South Africa. *Ther Clin Risk Manag* 2020;16:169–80.
13 Mokhele I, Mashamaite S, Majuba P, *et al*. Effective public-private partnerships for sustainable antiretroviral therapy: outcomes of the right to care health services GP down-referral program. *BMC Public Health* 2019;19:1471.
14 South African National Department of Health. Health indicators update: antiretroviral indicators, 2013. Available: https://www.uio.no/studier/emner/matnat/ifi/INF5761/v14/timeplan/artprogramme-overview-from-2004-to-2013_ndoh-2013.pdf [Accessed 20 Aug 2020].
15 Osler M, Hilderbrand K, Hennessey C, *et al*. A three-tier framework for monitoring antiretroviral therapy in high HIV burden settings. *J Int AIDS Soc* 2014;17:18908.
16 Osler M, Boulle A. Three Interlinked electronic registers (TIER.Net), 2010. Available: http://www.publichealth.uct.ac.za/sites/default/files/image_tool/images/108/TIER.Net %5B03 Nov 2010%5D.pdf [Accessed 10 Sep 2020].
17 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. who Guidel, 2013. Available: https://apps.who.int/iris/bitstream/handle/10665/85321/9789241505727_eng.pdf [Accessed 10 Sep 2020].
18 World Health Organization. March 2014 supplement to the 2013 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection, 2014. Available: https://apps.who.int/iris/handle/10665/104264
19 World Health Organization. Chapter 6: service delivery (consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection), 2015. Available: https://www.who.int/hiv/pub/arv/chapter6.pdf [Accessed 10 Sep 2020].
20 South African antiretroviral medicine. *South African antiretroviral treatment guidelines (adult*, 2015.
21 South African national department of health. National consolidated guidelines for the prevention of mother-to-child transmission of HIV (PMTCT) and the managment of HIV in children, adolescents and adults. *Dep Heal Repub South Africa* 2015:1–128.
22 WHO. Policy brief: consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection what ' S new, 2015. Available: https://www.who.int/publications/i/item/9789241549684
23 World Health Organization. Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2010, 2010. Available: https://apps.who.int/iris/bitstream/handle/10665/44443/9789241500395_eng.pdf;jsessionid=62C8E64E616E2F6C7B513FC6AB7F464F?sequence=1 [Accessed 10 Sep 2020].
24 Fox MP, Bor J, Brennan AT. Estimating retention in HIV care accounting for patient transfers: a national laboratory cohort study in South Africa. *PLoS Med* 2018;15.
25 Zanoni BC, Sibaya T, Cairns C, *et al*. Higher retention and viral suppression with adolescent-focused HIV clinic in South Africa. *PLoS One* 2017;12:e0190260.
26 Clouse K, Pettifor A, Maskew M, *et al*. Initiating antiretroviral therapy when presenting with higher CD4 cell counts results in reduced loss to follow-up in a resource-limited setting. *AIDS* 2013;27:645–50.
27 Ford N, Kranzer K, Hilderbrand K, *et al*. Early initiation of antiretroviral therapy and associated reduction in mortality, morbidity and defaulting in a nurse-managed, community cohort in Lesotho. *AIDS* 2010;24:2645–50.
28 Kluberg S, Fox MP, LaValley M. Single-pill art and retention in care: a regression discontinuity study in S Africa. *Top Antivir Med* 2018.
29 Hirasen K, Evans D, Maskew M, *et al*. The right combination - treatment outcomes among HIV-positive patients initiating first-line fixed-dose antiretroviral therapy in a public sector HIV clinic in Johannesburg, South Africa. *Clin Epidemiol* 2018;10:17–29.
30 Venter WDF, Moorhouse M, Sokhela S, *et al*. Dolutegravir plus two different prodrugs of tenofovir to treat HIV. *N Engl J Med* 2019;381:803–15.
31 Venter WDF, Sokhela S, Simmons B, *et al*. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate versus efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (advance): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV* 2020;7:e666–76.
32 Mushamiri I, Belai W, Sacks E, *et al*. Evidence on the effectiveness of community-based primary health care in improving HIV/AIDS outcomes for mothers and children in low- and middle-income countries: findings from a systematic review. *J Glob Health* 2021;11:11001.
33 Arnesen R, Moll AP, Shenoi SV. Predictors of loss to follow-up among patients on art at a rural hospital in KwaZulu-Natal, South Africa. *PLoS One* 2017;12:e0177168.
34 Yehia BR, Rebeiro P, Althoff KN, *et al*. Impact of age on retention in care and viral suppression. *J Acquir Immune Defic Syndr* 2015;68:413–9.
35 Yehia BR, Stephens-Shields AJ, Fleishman JA, *et al*. The HIV care continuum: changes over time in retention in care and viral suppression. *PLoS One* 2015;10:e0129376.

36 Bor J, Gage A, Onoya D. Variation in HIV care and treatment outcomes by facility in South Africa, 2011–2015: a cohort study. *PLoS Med* 2021.
37 Fox MP, Berhanu R, Steegen K, *et al*. Intensive adherence counselling for HIV-infected individuals failing second-line antiretroviral therapy in Johannesburg, South Africa. *Trop Med Int Health* 2016;21:1131–7.
38 Pasipamire L, Nesbitt RC, Ndlovu S, *et al*. Retention on art and predictors of disengagement from care in several alternative community-centred art refill models in rural Swaziland. *J Int AIDS Soc* 2018;21:e25183.
39 Mberi MN, Kuonza LR, Dube NM, *et al*. Determinants of loss to follow-up in patients on antiretroviral treatment, South Africa, 2004–2012: a cohort study. *BMC Health Serv Res* 2015;15.
40 Kanters S, Park JJH, Chan K, *et al*. Interventions to improve adherence to antiretroviral therapy: a systematic review and network meta-analysis. *Lancet HIV* 2017;4:e31–40.
41 Jobanputra K, Parker LA, Azih C, *et al*. Factors associated with virological failure and suppression after enhanced adherence counselling, in children, adolescents and adults on antiretroviral therapy for HIV in Swaziland. *PLoS One* 2015;10:e0116144.
42 Joseph Davey D, Abrahams Z, Feinberg M, *et al*. Factors associated with recent unsuppressed viral load in HIV-1-infected patients in care on first-line antiretroviral therapy in South Africa. *Int J STD AIDS* 2018;29:603–10.
43 UNAIDS. Ending AIDS progress towards the 90-90-90 targets. Glob AIDS update, 2017. Available: https://doi.org/UNAIDS/JC2900E
44 El-Sadr WM, Rabkin M, Nkengasong J, *et al*. Realizing the potential of routine viral load testing in sub-Saharan Africa. *J Int AIDS Soc* 2017;20 Suppl 7:e25010.
45 Mberi MN, Kuonza LR, Dube NM, *et al*. Determinants of loss to follow-up in patients on antiretroviral treatment, South Africa, 2004-2012: a cohort study. *BMC Health Serv Res* 2015;15:259.
46 Gumede SB, Venter WDF, Lalla-Edward ST. Understanding adherence in virally suppressed and unsuppressed human immunodeficiency virus-positive urban patients on second-line antiretroviral treatment. *South Afr J HIV Med* 2020;21:1107.
47 Andrieux-Meyer I, Calmy A, Cahn P, *et al*. Preferred antiretroviral drugs for the next decade of scale up. *J Int AIDS Soc* 2012;15:17986.
48 Rana AI, van den Berg JJ, Lamy E, *et al*. Using a mobile health intervention to support HIV treatment adherence and retention among patients at risk for disengaging with care. *AIDS Patient Care STDS* 2016;30:178–84.
49 Keene CM, Zokufa N, Venables EC, *et al*. 'Only twice a year': a qualitative exploration of 6-month antiretroviral treatment refills in adherence clubs for people living with HIV in Khayelitsha, South Africa. *BMJ Open* 2020;10:e037545.