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Uptake and 24-month outcomes of dolutegravir- versus lopinavir-based second-line antiretroviral therapy for people with HIV in South Africa: a retrospective cohort study and emulated target trial

[version 1]

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Abstract

Background

Aligning with the WHO, South Africa has replaced LPV/r with DTG in second-line ART after treatment failure with TDF/XTC/EFV. Initial guidance included special considerations for DTG use among women.

Methods

We analysed routine de-identified data of adults switched from TDF/XTC/EFV to second-line AZT/XTC/LPV/r, AZT/XTC/DTG, or TDF/XTC/DTG between December 2019 and December 2023 at 108 healthcare facilities in KwaZulu-Natal, South Africa. Among people switched before July 2021, we emulated a target trial comparing 24-month death or loss to follow-up (LTFU), and viraemia (>50 copies/mL). We conducted intention-to-treat and per-protocol analyses using weighted logistic regression with bootstrapped CIs.

Results

Overall, women were less likely than men to switch to DTG (RR: 0.92 [95% CI: 0.88, 0.96]; N=3649). Of 2321 people switched before July 2021, 915 (39%) switched to AZT/XTC/LPV/r, 415 (18%) to AZT/XTC/DTG, and 991 (43%) to TDF/XTC/DTG. Median age was 36 years (IQR: 30, 43) and 1364 (59%) were women. In intention-to-treat analyses, the standardised 24-month risk of death or LTFU was similar with AZT/XTC/LPV/r (31%), AZT/XTC/DTG (30%), and TDF/XTC/DTG (34%). The standardised risk of 24-month viraemia among those retained in care with a viral load result (N=1270) was higher with AZT/XTC/LPV/r (49%) than with AZT/XTC/DTG (39%; aRD: -11% [95% CI -17%, -4%]) or TDF/XTC/DTG (38%; aRD: -11% [95% CI -17%, -4%]). Per-protocol analyses gave similar results.

Conclusions

While retention was similar across regimens, viraemia was less common on DTG-based ART, supporting current guidelines.

Keywords
antiretroviral therapy, retention in care, viral load, dolutegravir, ritonavir-boosted lopinavir, tenofovir

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Summary
A target trial emulation including adults switched from TDF/XTC/EFV to second-line AZT/XTC/LPV/r, AZT/XTC/DTG, or TDF/XTC/DTG in a South African HIV cohort (N=2321) showed similar 24-month outcomes of death or loss to follow-up but less viraemia on DTG-based ART.

Introduction
Since 2018, the World Health Organization has recommended antiretroviral therapy (ART) containing dolutegravir (DTG) as the preferred second-line regimen upon treatment failure with a regimen containing efavirenz (EFV), replacing ritonavir-boosted lopinavir (LPV/r) in second-line ART.[1,2] This recommendation was informed by the DAWNING trial, which showed superior 48-week viral suppression with DTG- compared with LPV/r-based second-line ART.[3] The NADIA trial subsequently showed recycling tenofovir disoproxil fumarate (TDF) from first-line ART in second-line DTG-based regimens was non-inferior to changing to zidovudine (AZT) at 48 and 96 weeks post switch.[4,5]

In South Africa, DTG was rolled out for use in first- and second-line ART in December 2019. In first-line ART, DTG was associated with better clinical outcomes than EFV as the former standard of care.[6] In the early stages of the rollout, women were less likely than men to receive first-line DTG due to initial safety concerns regarding DTG in early pregnancy, though this difference declined over time with newer evidence and updated guidelines recommending DTG-based ART also for adolescent girls and women of childbearing potential.[1,6] However, there is little data regarding uptake of second-line DTG by gender. For second-line ART, previous analyses of routinely collected primary care data in South Africa showed superior 12-month retention in care with AZT/lamivudine or emtricitabine (XTC) /DTG compared with either AZT/XTC/LPV/r or TDF/XTC/DTG, and superior 12-month viral suppression with either DTG-based second-line regimen than with AZT/XTC/LPV/r.[7]

While these data are encouraging, continued monitoring with longer-term follow-up in large, routine care datasets remains essential, especially in light of recent reports of emergent DTG resistance.[8–10] Therefore, we aimed to assess uptake of DTG-based ART by gender, and subsequent 24-month outcomes between second-line AZT/XTC/LPV/r, AZT/XTC/DTG, or TDF/XTC/DTG in routine care settings in South Africa.

Methods
Study design and setting
We used de-identified, routinely collected data from South Africa's ART programme. We included data from 108 public sector primary healthcare clinics in the eThekwini Municipality and uMgungundlovu district in KwaZulu-Natal province, South Africa in this analysis.

We created an uptake and an outcome cohort, with the latter having an earlier cut-off for regimen switches allowing sufficient time to ascertain outcomes. In the outcome cohort, we emulated a target trial to compare death and loss to follow-up (LTFU) through 24 months, and viraemia at 24 months, by second-line regimen. The prespecified protocol of the target trial as well as key components of how it was emulated are described in Table 1.

Table 1. Specification of the target trial and emulated trial. ART: antiretroviral therapy; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; LPV/r: ritonavir-boosted lopinavir; LTFU: loss to follow-up; TDF: tenofovir disoproxil fumarate; XTC: lamivudine or emtricitabine.

Protocol	Target trial	Emulated trial
Eligibility criteria	Taking TDF/XTC/EFV and due to switch to TDF/XTC/DTG, AZT/XTC/DTG, or AZT/XTC/LPV/r	Switched from TDF/XTC/EFV to TDF/XTC/DTG, AZT/XTC/DTG, or AZT/XTC/LPV/r
	Confirmed virological failure, defined as two consecutive viral loads ≥1000 copies/mL and taken 56-450 days apart (intercurrent viral loads within 56 days are permitted if they are also ≥1000 copies/mL), with the latter occurring ≤450 days before enrolment	Switch occurred after confirmed virological failure, defined as two consecutive viral loads ≥1000 copies/mL and taken 56-450 days apart (intercurrent viral loads within 56 days are permitted if they are also ≥1000 copies/mL), with the latter occurring ≤450 days before the switch
	Eligibility to switch during study period	Switch occurred between 1 December 2019 (start of availability of DTG) and 30 June 2021 (allowing 30 months' of follow-up until data closure on 31 December 2023)
	No known prior PI or INSTI exposure	Same

Table 1. *Continued*

Protocol	Target trial	Emulated trial
	Age ≥15 years at switch	Same
	Not pregnant at switch	Same
	In care in a study site	In care in a facility with available data through 31 December 2023
Treatment strategies	Switch to TDF/XTC/DTG	Same
	Switch to AZT/XTC/DTG	Same
	Switch to AZT/XTC/LPV/r	Same
Treatment assignment	Participants are randomly assigned and are aware of the strategy they are assigned to (open-label).	Randomisation is assumed conditional on baseline covariates used in inverse probability weighting[a].
Follow-up period	24 months for death and LTFU outcomes and 30 months for viral load outcome.	Same
Outcomes: primary endpoints	Death or LTFU through 24 months.	Same. The date of LTFU is defined as the midpoint between the last attended visit and the first visit missed by ≥90 days[b].
	24-month viraemia, defined as having a viral load >50 copies/mL among those retained in care and with a 24-month viral load result (window: 18-30 months; using the closest viral load to 24 months).	Same
Outcomes: sensitivity analysis	Death, LTFU, or transfer-out through 24 months.	Same
	24-month viraemia, defined as having a viral load ≥1000 copies/mL among those retained in care and with a 24-month viral load result (window: 18-30 months; using the closest viral load to 24 months).	Same
Causal contrasts	Intention-to-treat analysis. Participants are censored upon transfer-out.	Observational analogue thereof
	Per-protocol analysis. Participants are censored upon transfer-out or regimen change.	Observational analogue thereof
Statistical analysis	In intention to treat analysis, death or LTFU is assessed through pooled logistic regression. Viraemia is assessed through logistic regression among people retained in care with a 24-month viral load result.	Same with inverse probability of treatment weighting as described above to emulate randomisation.
	In per-protocol analysis, death or LTFU is assessed through pooled logistic regression with inverse probability weighting of censoring, using baseline[a] and time-varying[c] covariates. Viraemia is assessed through logistic regression among people retained in care with a 24-month viral load result, weighted for inverse probability of censoring (assessed with baseline[a] and time-varying[c] covariates) as well as inverse probability of not having a 24-month viral load measurement (assessed with baseline covariates[a]).	Same with additional inverse probability of treatment weighting as described above to emulate randomisation.

[a]Categorical baseline covariates: gender, age, calendar time of switch, region, prior decentralised ART, last viral load before switch, last CD4 cell count before switch, previously having missed a visit by ≥90 days, facility retention category (proportion of people in care in the facility with a missed visit in the year prior to the start of study enrolment; facilities categorised in quintiles). Continuous baseline covariates: days since first consecutive viral load ≥1000 copies/mL.
[b]Different intervals between clinic visits (generally ranging from one to six months) could bias outcomes if the date of LTFU were set as the date of the last attended or first missed visit. To account for this, the date of LTFU is defined as the midpoint between the last attended visit and the first visit missed by ≥90 days, and the endpoint is reached if this LTFU date is within 24 months of switching. With maximal visit intervals of six months, the missed visit would have to be scheduled within 3 months of the end of follow-up for the LTFU date to fall within the 24 months' follow-up period. Ascertainment of whether this visit was missed would require an additional 90 days. Thus, 30 months between switch and data closure are sufficient to ascertain 24-month LTFU.
[c]Categorical time-varying covariates: pregnancy, tuberculosis, receiving decentralised ART (less-frequent clinic visits). Continuous time-varying covariates: months since switch, square of months since switch.

This study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines and in alignment with emerging recommendations on reporting target trial emulation.[11–16]

Participants

In the uptake cohort, we included people ≥15 years of age who switched from TDF/XTC/EFV to AZT/XTC/LPV/r, AZT/XTC/DTG, or TDF/XTC/DTG between 1 December 2019 (the start of DTG availability) and 31 December 2023 (data closure) following confirmed virological failure. Confirmed virological failure was defined as two consecutive viral loads ≥1000 copies/mL taken 56-450 days apart. We excluded people whose most recent virologic failure was >450 days before the switch, who had known prior exposure to a protease or integrase strand transfer inhibitor, who were pregnant at the time of switch, and who transferred out on the day of the regimen switch.

In the outcome cohort, we applied the same eligibility criteria except that the switch had to occur by 30 June 2021, allowing 30 months for outcome ascertainment (see Table 1 for rationale).

Outcome measures and exposures

In the uptake cohort, the main outcome of interest was the risk of receiving DTG-based ART, i.e. either of the DTG-containing regimens. The main exposure of interest was gender.

In the outcome cohort, the co-primary endpoints were i) time to death or LTFU through 24 months after switch, and ii) the risk of 24-month viraemia. The date of LTFU was defined as the midpoint between the last attended visit and the scheduled date of the first visit missed by at least 90 days. People who transferred out of their facility were censored at the date of transfer. Those remaining in care were censored at 24 months post switch. The viraemia endpoint was defined as having a viral load >50 copies/mL 24 months (window: 18-30 months) after switch. If several viral load results were recorded within this window, we selected the result closest to 24 months. The main exposure of interest was the second-line regimen initiated at switch, i.e. AZT/XTC/LPV/r, AZT/XTC/DTG, or TDF/XTC/DTG.

In sensitivity analyses, we assessed a composite of death, LTFU, and transfer-out, and defined 24-month viraemia as ≥1000 copies/mL.

Data sources/measurement

We used de-identified data from South Africa's TIER. Net electronic database, which contains demographic data, clinical status (including date of death or transfer-out), ART regimen, clinic visit information, and viral load outcomes of people receiving ART in public sector healthcare facilities.[17]

Statistical methods

In the uptake cohort, we used Poisson regression with robust standard errors to assess the relative risk (RR) of switching to DTG-based ART by gender. We tested for interaction between gender and age and between gender and calendar period of switch (before or after June 2021, when South African guidelines recommended DTG for all) using likelihood ratio tests.

To assess treatment outcomes by second-line ART regimen in the outcome cohort, we conducted intention-to-treat and per-protocol analyses for both co-primary endpoints after emulating randomisation using inverse probability of treatment weights (IPTWs).

In intention-to-treat analysis for the co-primary endpoint of death or LTFU, we estimated hazard ratios using pooled logistic regression with IPTWs. Using this model, we derived the standardised monthly hazards of death or LTFU for each treatment assuming all participants received the treatment. We then calculated the standardised 24-month risk for each treatment from the monthly hazards through 24 months. Per-protocol analysis was the same, except that we censored at regimen change and weighted by the product of the IPTWs and inverse probability of censoring weights (IPCWs).

Viraemia was assessed in intention-to-treat analysis through logistic regression with IPTWs. Implicitly, this analysis assesses viraemia among people who were retained in care and had a 24-month viral load result. By contrast, the per-protocol analysis weighted for the inverse probability of censoring due to non-retention (transfer-out, death, or LTFU) or regimen change through 24 months (derived from longitudinal data), the inverse probability of not having a 24-month viral load result, and the IPTW.

We used multinomial logistic regression, with the treatment as the outcome and baseline variables as covariates, to calculate propensity scores, and stabilised IPTWs, which we used in all outcome models to emulate randomisation. To calculate IPCWs, which were used in per-protocol models, we ran pooled logistic regressions with censoring as the

outcome and calculated the 24-month risk of censoring through monthly hazards through 24 months. We stabilised IPCWs by dividing the 24-month risk obtained only baseline covariates (numerator) by the 24-month risk obtained with baseline and time-varying covariates in the regression (denominator).[18] Finally, for the per-protocol analysis of 24-month viraemia, we assessed the inverse probability of not having a 24-month viral load result through logistic regression using baseline covariates. We stabilised weights by multiplying the inverse probability by the overall proportion of participants without a 24-month viral load result. The IPTWs, IPCWs, and inverse probability weights for not having a 24-month viral load result were all stabilised and truncated at the first and 99th centile. Further information on the covariates included in each model is available in Table 1.

Sensitivity analyses were conducted as described for the primary endpoints.

For descriptive outcomes, we report categorical variables with frequencies and percentages, and continuous variables with medians and interquartile ranges (IQRs). For inferential outcomes, we report standardised risks, adjusted risk differences (aRDs), and RRs with 95% confidence intervals (CIs).

Analyses were conducted in R version 4.4.0.

Ethics

The cohort study within which this work was conducted was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE646/17; latest approval 13.02.2025), the KwaZulu-Natal Provincial Health Research Ethics Committee (KZ_201807_021; 20.01.2025), the eThekwini Municipality Health Unit (05.03.2024), the uMkhanyakude District Health Office (16.05.2024) and the uMgungundlovu District Health Office (19.02.2025), with a waiver of consent for analysis of de-identified, routinely collected data. This research was conducted in alignment with the Declaration of Helsinki.

Results

Participant characteristics in the uptake cohort

Between 1 December 2019 and 31 December 2023, 3814 people taking TDF/XTC/EFV switched to AZT/XTC/LPV/r, AZT/XTC/DTG, or TDF/XTC/DTG after virological failure. We excluded 165 participants who were <15 years old, had prior exposure to protease or integrase strand transfer inhibitors, were pregnant at switch, or transferred out on the day of the regimen switch. The remaining 3649 participants were included in the uptake cohort (Figure 1); 998 (27%) switched to AZT/XTC/LPV/r, 711 (19%) to AZT/XTC/DTG, and 1940 (53%) TDF/XTC/DTG. 2292 (63%) were women, median age at switch was 36 years (IQR 29, 42), and median known time with viraemia ≥1000 copies/mL was 397 days (IQR 251, 650; Table 2).

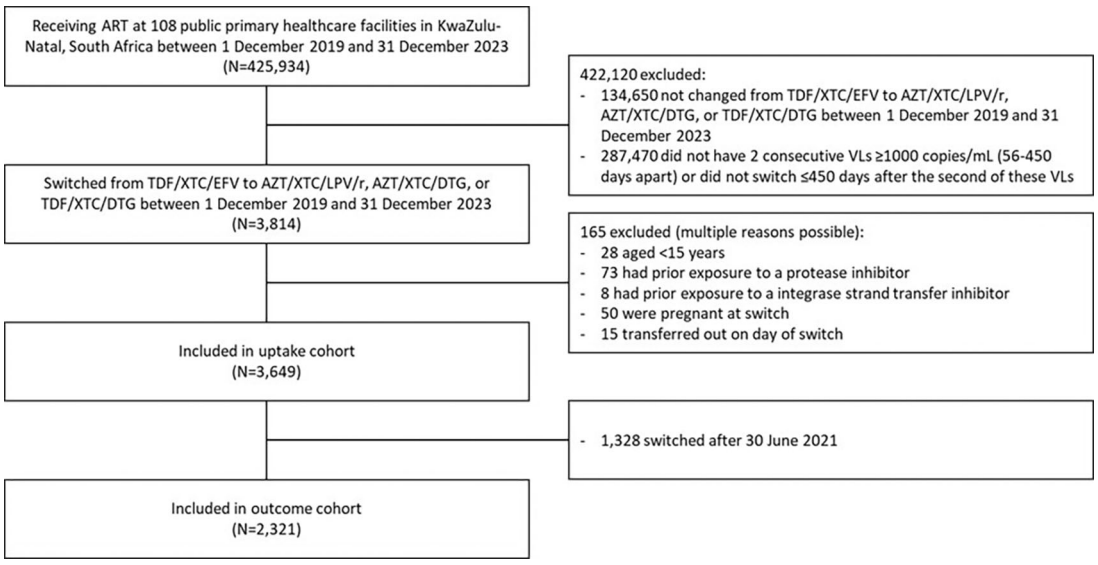

Figure 1. Flow diagram. ART: antiretroviral therapy; AZT: zidovudine; DTG: dolutegravir; EFV: efavirenz; LPV/r: ritonavir-boosted lopinavir; TDF: tenofovir disoproxil fumarate; VL: viral load; XTC: lamivudine or emtricitabine.

Table 2. Baseline characteristics in the uptake cohort. Categorical variables are shown as n (%) and continuous variables as median (IQR). ART: antiretroviral therapy; AZT: zidovudine; DTG: dolutegravir; LPV/r: ritonavir-boosted lopinavir; TDF: tenofovir disoproxil fumarate; XTC: lamivudine or emtricitabine.

Characteristic	Overall N = 3,649	AZT/XTC/LPV/r N = 998	AZT/XTC/DTG N = 711	TDF/XTC/DTG N = 1,940
Women	2,292 (63%)	679 (68%)	435 (61%)	1,178 (61%)
Age in years	36 (29, 42)	36 (30, 42)	36 (30, 42)	36 (29, 42)
15-29	917 (25%)	240 (24%)	167 (23%)	510 (26%)
30-44	2,049 (56%)	587 (59%)	405 (57%)	1,057 (54%)
≥45	683 (19%)	171 (17%)	139 (20%)	373 (19%)
Receiving tuberculosis treatment	57 (1.6%)	15 (1.5%)	17 (2.4%)	25 (1.3%)
Region				
eThekwini Metropolitan Municipality	2,084 (57%)	631 (63%)	432 (61%)	1,021 (53%)
uMgungundlovu District Municipality	1,565 (43%)	367 (37%)	279 (39%)	919 (47%)
Years since ART initiation	4.0 (2.1, 6.9)	3.3 (1.7, 6.4)	4.2 (2.1, 7.2)	4.3 (2.3, 7.1)
CD4 cell count at ART initiation in cells/μL^3 [a]	200 (105, 320)	170 (90, 290)	170 (90, 300)	220 (120, 350)
<200	1,251 (48%)	410 (56%)	263 (55%)	578 (41%)
200-349	795 (30%)	199 (27%)	132 (27%)	464 (33%)
350-499	343 (13%)	81 (11%)	61 (13%)	201 (14%)
≥500	219 (8.4%)	43 (5.9%)	26 (5.4%)	150 (11%)
Missing	1,041	265	229	547
Days from CD4 count at ART initiation to ART initiation	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Missing	1,041	265	229	547
Most recent CD4 cell count in cells/μL^3 [b]	280 (160, 450)	250 (130, 420)	250 (120, 400)	300 (170, 470)
<200	834 (33%)	250 (37%)	198 (38%)	386 (29%)
200-349	707 (28%)	181 (27%)	149 (28%)	377 (28%)
350-499	487 (19%)	130 (19%)	88 (17%)	269 (20%)
≥500	509 (20%)	110 (16%)	89 (17%)	310 (23%)
Missing	1,112	327	187	598
Days from most recent CD4 result to switch	279 (74, 693)	241 (61, 635)	210 (55, 589)	314 (112, 792)
Missing	1,112	327	187	598
Prior exposure to AZT	35 (1.0%)	6 (0.6%)	12 (1.7%)	17 (0.9%)
Prior referral to decentralised ART	775 (21%)	170 (17%)	151 (21%)	454 (23%)
Last viral load in copies/mL				
1'000-9'999	1,533 (42%)	367 (37%)	252 (35%)	914 (47%)
10'000-99'999	1,481 (41%)	415 (42%)	312 (44%)	754 (39%)
≥100'000	635 (17%)	216 (22%)	147 (21%)	272 (14%)
Days from last viral load to switch	84 (42, 156)	67 (35, 120)	61 (31, 113)	100 (56, 188)
Days with viraemia ≥1000 copies/mL in all consecutive measurements	397 (251, 650)	371 (231, 604)	364 (235, 587)	426 (273, 688)
Any prior visit missed by ≥90 days	1,331 (36%)	283 (28%)	264 (37%)	784 (40%)

Table 2. *Continued*

Characteristic	Overall N = 3,649	AZT/XTC/LPV/r N = 998	AZT/XTC/DTG N = 711	TDF/XTC/DTG N = 1,940
Year of switch				
2019/2020	1,878 (51%)	801 (80%)	292 (41%)	785 (40%)
2021	782 (21%)	157 (16%)	246 (35%)	379 (20%)
2022	607 (17%)	31 (3.1%)	146 (21%)	430 (22%)
2023	382 (10%)	9 (0.9%)	27 (3.8%)	346 (18%)
Facility-level retention				
First (lowest) quintile	686 (19%)	188 (19%)	144 (20%)	354 (18%)
Second quintile	766 (21%)	252 (25%)	155 (22%)	359 (19%)
Third quintile	780 (21%)	231 (23%)	151 (21%)	398 (21%)
Fourth quintile	705 (19%)	197 (20%)	103 (14%)	405 (21%)
Fifth (highest) quintile	712 (20%)	130 (13%)	158 (22%)	424 (22%)

[a]Closest CD4 cell count to ART initiation within ≤180 days before to ≤30 days after ART initiation.
[b]Most recent CD4 cell count before switch to second-line ART and >30 days after ART initiation.

Observed switches and effect of gender

The number of monthly switches increased from 57 in December 2019 to 265 in June 2020, before dropping to below 50 for all months after November 2022 (Figure 2A). AZT/XTC/LPV/r was the most frequently selected second-line regimen until May 2020, when TDF/XTC/DTG became the most-used regimen at switch (Figure 2B).

The RR for women (compared with men) to receive a DTG-based regimen was 0.92 (95% CI 0.88, 0.96). We found no evidence that the effect of gender on DTG use was modified by age category (interaction term p=0.83; Table 3), whereas the RR for women to receive DTG was lower in December 2019 – May 2021 (0.80; 95% CI 0.75, 0.85) and subsequently equalised in June 2021 – December 2023 (0.97; 95% CI 0.95, 1.00; interaction term p=0.013; Table 3).

Participant characteristics in the outcome cohort

Of the 3649 participants in the uptake cohort, 2321 switched before 30 June 2021 and were included in the outcome cohort (Figure 1). Of these, 915 (39%) switched to AZT/XTC/LPV/r, 415 (18%) to AZT/XTC/DTG, and 991 (43%) to TDF/XTC/DTG. Overall, 1364 (59%) were women, median age at switch was 36 years (IQR: 30, 43), and median known

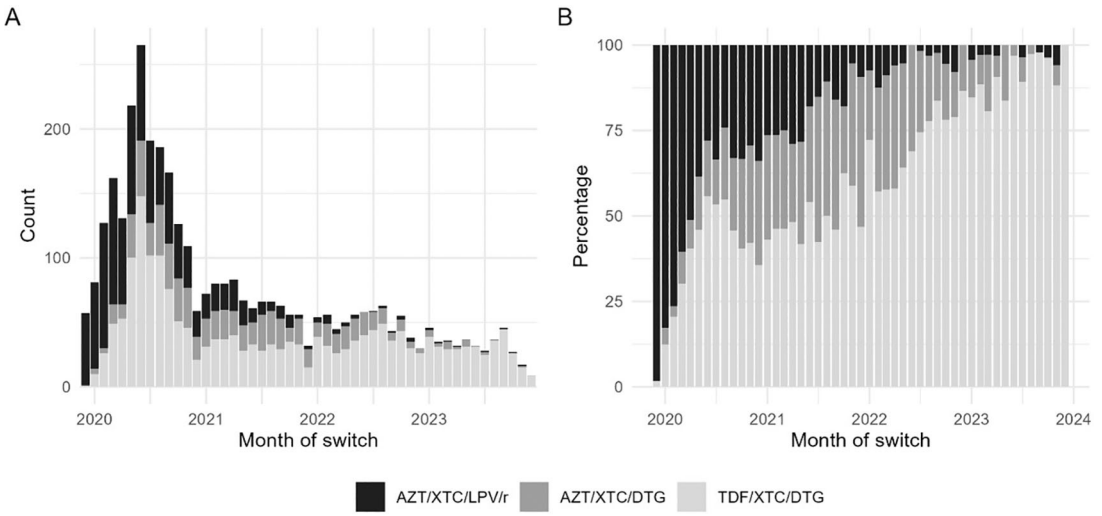

Figure 2. Switches to second-line ART over time. A. Number of switches to each second-line regimen per month. B. Percentage of switches to each second-line regimen per month. ART: antiretroviral therapy; AZT: zidovudine; DTG: dolutegravir; LPV/r: ritonavir-boosted lopinavir; TDF: tenofovir disoproxil fumarate; XTC: lamivudine or emtricitabine.

Table 3. Relative risk for women to switch to DTG-based ART in the uptake cohort. N=3649. CI: confidence interval; DTG: dolutegravir; RR: relative risk.

	Proportion of men switched to DTG	Proportion of women switched to DTG	RR (95% CI)
Overall			
	1038/1357 (76%)	1613/2292 (70%)	0.92 (0.88, 0.96)
By age[a]			
15-29 years	164/215 (76%)	513/702 (73%)	0.96 (0.88, 1.05)
30-44 years	589/782 (75%)	873/1267 (69%)	0.91 (0.87, 0.97)
≥45 years	285/360 (79%)	227/323 (70%)	0.89 (0.81, 0.97)
By calendar period[b]			
December 2019 – May 2021	637/935 (68%)	719/1325 (54%)	0.80 (0.75, 0.85)
June 2021 – December 2023	401/422 (95%)	894/967 (92%)	0.97 (0.95, 1.00)

[a]Likelihood ratio test for interaction term between gender and age: p=0.83.
[b]Likelihood ratio test for interaction term between gender and calendar period: p=0.013.

time with a viral load ≥1000 copies/mL was 371 days (IQR: 236, 581). After applying IPTWs, groups were balanced for baseline characteristics (Table 4).

Death and LTFU

In the outcome cohort, the crude proportion of death or LTFU was 283/915 (31%) with AZT/XTC/LPV/r, 117/415 (28%) with AZT/XTC/DTG, and 320/991 (32%) with TDF/XTC/DTG. This included three (0%), 9 (2%), and 17 (2%) deaths, respectively. Facility transfers were recorded for 52/915 (6%) with AZT/XTC/LPV/r, 22/415 (5%) with AZT/XTC/DTG, and 52/991 (5%) with TDF/XTC/DTG. Regimen changes were recorded for 200/915 (22%) in the AZT/XTC/LPV/r, 95/415 (23%) in the AZT/XTC/DTG, and 147/991 (15%) in the TDF/XTC/DTG group (Table 5).

In intention-to-treat analysis, the standardised 24-month risk of death or LTFU was similar between regimens at 31% (95% CI: 27%, 34%) with AZT/XTC/LPV/r, 30% (95% CI: 24%, 35%) with AZT/XTC/DTG (aRD to AZT/XTC/LPV/r: -1% [95% CI: -8%, 5%]), and 34% (95% CI: 31%, 37%) with TDF/XTC/DTG (aRD to AZT/XTC/LPV/r: 3% [95% CI: -2%, 8%]; aRD to AZT/XTC/DTG: 4% [95% CI: -2%, 11%]; Table 6).

In per-protocol analysis, standardised risks were similar at 31% (95% CI: 27%, 34%) with AZT/XTC/LPV/r, 27% (95% CI: 21%, 32%) with AZT/XTC/DTG (aRD to AZT/XTC/LPV/r: -4% [95% CI: -11%, 2%), and 34% (95% CI: 31%, 37%) with TDF/XTC/DTG (aRD to AZT/XTC/LPV/r: 3% [95% CI: -2%, 8%]; aRD to AZT/XTC/DTG: 7% [95% CI: 1%, 13%]; Table 6).

Viraemia

A 24-month viral load result was available for 521/915 (57%) in the AZT/XTC/LPV/r group, 240/415 (58%) in the AZT/XTC/DTG group, and 509/991 (51%) in the TDF/XTC/DTG group. This corresponds to 521/580 (90%), 240/276 (87%), and 509/619 (82%), respectively, of those retained in care at 24 months. The median time from baseline to the 24-month viral load result was 727 days (IQR: 668, 787) and was similar between groups. Among available 24-month viral loads, 249/521 (48%) in the AZT/XTC/LPV/r group, 94/240 (39%) in the AZT/XTC/DTG group, and 188/509 (37%) in the TDF/XTC/DTG group were viraemic (Table 5).

In intention-to-treat analysis, the standardised risk of viraemia at 24 months among people retained in care with a 24-month viral load result was higher with AZT/XTC/LPV/r (49% [95% CI: 45%, 54%]) than with AZT/XTC/DTG (39% [95% CI: 31%, 46%]; aRD: -11% [95% CI: -17%, -4%]) or TDF/XTC/DTG (38% [95% CI: 33%, 43%]; aRD: -11% [95% CI: -17%, -4%]), but similar between AZT/XTC/DTG and TDF/XTC/DTG (aRD: 0% [95% CI: -10%, 8%]; Table 6).

Similarly, in per-protocol analysis the standardised risk was 52% (95% CI: 46%, 58%) in the AZT/XTC/LPV/r group, 38% (95% CI: 29%, 46%) in the AZT/XTC/DTG group (aRD to AZT/XTC/LPV/r: -13% [95% CI: -25%, -4%]), and 38% (95% CI 32%, 42%) in the TDF/XTC/DTG group (aRD to AZT/XTC/LPV/r: -14% [95% CI: -23%, -7%]; aRD to AZT/XTC/DTG: -1% [95% CI: -9%, 9%; Table 6).

Table 4. Baseline characteristics in the outcome cohort and the outcome cohort pseudo-population after IPTW. Categorical variables are shown as n (%) and continuous variables as median (IQR). ART: antiretroviral therapy; AZT: zidovudine; DTG: dolutegravir; IPTW: inverse probability of treatment weighting; LPV/r: ritonavir-boosted lopinavir; TDF: tenofovir disoproxil fumarate; XTC: lamivudine or emtricitabine.

	Outcome cohort				Outcome cohort pseudo-population after IPTW			
Characteristic	**Overall N = 2,321**	**AZT/XTC/LPV/r N = 915**	**AZT/XTC/DTG N = 415**	**TDF/XTC/DTG N = 991**	**Overall N = 2,307**	**AZT/XTC/LPV/r N = 911**	**AZT/XTC/DTG N = 406**	**TDF/XTC/DTG N = 991**
Women	1,364 (59%)	614 (67%)	219 (53%)	531 (54%)	1,353 (59%)	536 (59%)	239 (59%)	579 (58%)
Age in years	36 (30, 43)	36 (30, 42)	36 (30, 43)	36 (30, 43)	36 (30, 43)	36 (30, 43)	35 (30, 42)	36 (30, 43)
15-29	557 (24%)	221 (24%)	94 (23%)	242 (24%)	545 (24%)	210 (23%)	101 (25%)	234 (24%)
30-44	1,325 (57%)	539 (59%)	238 (57%)	548 (55%)	1,327 (58%)	527 (58%)	235 (58%)	565 (57%)
≥45	439 (19%)	155 (17%)	83 (20%)	201 (20%)	435 (19%)	174 (19%)	69 (17%)	192 (19%)
Receiving tuberculosis treatment	37 (1.6%)	14 (1.5%)	12 (2.9%)	11 (1.1%)	33 (1.4%)	14 (1.5%)	9 (2.2%)	11 (1.1%)
Region								
eThekwini Metropolitan Municipality	1,304 (56%)	579 (63%)	243 (59%)	482 (49%)	1,291 (56%)	508 (56%)	219 (54%)	564 (57%)
uMgungundlovu District Municipality	1,017 (44%)	336 (37%)	172 (41%)	509 (51%)	1,017 (44%)	403 (44%)	187 (46%)	427 (43%)
Years since ART initiation	3.23 (1.68, 6.03)	3.21 (1.63, 6.00)	3.39 (1.57, 6.69)	3.18 (1.75, 5.86)	3.26 (1.69, 5.98)	3.38 (1.70, 5.98)	3.53 (1.65, 6.52)	3.05 (1.69, 5.73)
CD4 cell count at ART initiation in cells/μL^3 [a]	190 (100, 310)	170 (90, 290)	150 (80, 250)	220 (120, 340)	190 (100, 300)	170 (90, 290)	160 (90, 260)	210 (110, 330)
<200	871 (52%)	385 (56%)	173 (60%)	313 (44%)	881 (52%)	373 (55%)	170 (58%)	337 (46%)
200-349	486 (29%)	185 (27%)	73 (25%)	228 (32%)	495 (29%)	194 (29%)	76 (26%)	224 (31%)
350-499	205 (12%)	75 (11%)	28 (9.7%)	102 (14%)	200 (12%)	70 (10%)	29 (10.0%)	100 (14%)
≥500	124 (7.4%)	38 (5.6%)	15 (5.2%)	71 (9.9%)	126 (7.4%)	43 (6.2%)	16 (5.6%)	67 (9.2%)
Missing	635	232	126	277	606	231	114	261
Days from CD4 count at ART initiation to ART initiation	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Missing	635	232	126	277	606	231	114	261

Table 4. *Continued*

	Outcome cohort				Outcome cohort pseudo-population after IPTW			
Characteristic	**Overall N = 2,321**	**AZT/XTC/LPV/r N = 915**	**AZT/XTC/DTG N = 415**	**TDF/XTC/DTG N = 991**	**Overall N = 2,307**	**AZT/XTC/LPV/r N = 911**	**AZT/XTC/DTG N = 406**	**TDF/XTC/DTG N = 991**
Most recent CD4 cell count in cells/μL^{3} [b]	260 (140, 420)	250 (130, 430)	230 (100, 380)	280 (165, 450)	260 (150, 430)	250 (140, 430)	260 (130, 420)	260 (160, 430)
<200	575 (25%)	232 (25%)	133 (32%)	210 (21%)	549 (24%)	220 (24%)	98 (24%)	232 (23%)
200-349	447 (19%)	164 (18%)	84 (20%)	199 (20%)	459 (20%)	180 (20%)	83 (20%)	196 (20%)
350-499	296 (13%)	117 (13%)	50 (12%)	129 (13%)	284 (12%)	113 (12%)	53 (13%)	118 (12%)
≥500	283 (12%)	101 (11%)	44 (11%)	138 (14%)	273 (12%)	103 (11%)	44 (11%)	126 (13%)
Missing	720 (31%)	301 (33%)	104 (25%)	315 (32%)	743 (32%)	295 (32%)	128 (32%)	320 (32%)
Days from most recent CD4 result to switch	218 (58, 508)	228 (56, 586)	145 (47, 473)	234 (71, 495)	227 (61, 545)	231 (58, 605)	152 (56, 513)	236 (71, 508)
Missing	720	301	104	315	743	295	128	320
Prior exposure to AZT	24 (1.0%)	6 (0.7%)	7 (1.7%)	11 (1.1%)	26 (1.1%)	8 (0.9%)	6 (1.6%)	12 (1.2%)
Prior referral to decentralised ART	427 (18%)	152 (17%)	84 (20%)	191 (19%)	458 (20%)	175 (19%)	98 (24%)	185 (19%)
Last viral load in copies/mL								
1'000-9'999	917 (40%)	329 (36%)	132 (32%)	456 (46%)	908 (39%)	360 (40%)	162 (40%)	385 (39%)
10'000-99'999	969 (42%)	384 (42%)	192 (46%)	393 (40%)	960 (42%)	379 (42%)	168 (41%)	412 (42%)
≥100'000	435 (19%)	202 (22%)	91 (22%)	142 (14%)	440 (19%)	172 (19%)	75 (19%)	193 (19%)
Days from last viral load to switch	76 (36, 139)	65 (33, 117)	59 (30, 110)	91 (52, 174)	73 (37, 133)	65 (35, 117)	59 (32, 112)	87 (49, 168)
Days with viraemia ≥1000 copies/mL in all consecutive measurements	371 (236, 581)	363 (230, 579)	342 (224, 563)	391 (254, 595)	377 (238, 594)	378 (235, 604)	351 (225, 563)	380 (251, 597)
Any prior visit missed by ≥90 days	624 (27%)	243 (27%)	117 (28%)	264 (27%)	619 (27%)	240 (26%)	111 (27%)	268 (27%)
Quarter of switch								
Q4 2019/Q1 2020	427 (18%)	318 (35%)	23 (5.5%)	86 (8.7%)	454 (20%)	176 (19%)	69 (17%)	209 (21%)
Q2 2020	614 (26%)	225 (25%)	88 (21%)	301 (30%)	485 (21%)	194 (21%)	95 (23%)	196 (20%)
Q3 2020	543 (23%)	164 (18%)	99 (24%)	280 (28%)	478 (21%)	190 (21%)	89 (22%)	199 (20%)
Q4 2020	294 (13%)	94 (10%)	82 (20%)	118 (12%)	461 (20%)	178 (20%)	79 (19%)	204 (21%)
Q1/Q2 2021	443 (19%)	114 (12%)	123 (30%)	206 (21%)	429 (19%)	173 (19%)	75 (18%)	182 (18%)

Table 4. *Continued*

Characteristic	Outcome cohort				Outcome cohort pseudo-population after IPTW			
	Overall N = 2,321	AZT/XTC/LPV/r N = 915	AZT/XTC/DTG N = 415	TDF/XTC/DTG N = 991	Overall N = 2,307	AZT/XTC/LPV/r N = 911	AZT/XTC/DTG N = 406	TDF/XTC/DTG N = 991
Facility-level retention								
First (lowest) quintile	431 (19%)	171 (19%)	87 (21%)	173 (17%)	424 (18%)	169 (19%)	69 (17%)	186 (19%)
Second quintile	491 (21%)	229 (25%)	93 (22%)	169 (17%)	603 (26%)	239 (26%)	108 (27%)	256 (26%)
Third quintile	479 (21%)	216 (24%)	73 (18%)	190 (19%)	543 (24%)	214 (23%)	97 (24%)	232 (23%)
Fourth quintile	478 (21%)	180 (20%)	54 (13%)	244 (25%)	285 (12%)	112 (12%)	51 (13%)	122 (12%)
Fifth (highest) quintile	442 (19%)	119 (13%)	108 (26%)	215 (22%)	453 (20%)	177 (19%)	81 (20%)	196 (20%)

[a]Closest CD4 cell count to ART initiation within ≤180 days before to ≤30 days after ART initiation.
[b]Most recent CD4 cell count before switch to second-line ART and >30 days after ART initiation; missing category included in models.

Table 5. Crude outcomes. AZT: zidovudine; CI: confidence interval; DTG: dolutegravir; IQR: interquartile range; LTFU: loss to follow-up; TDF: tenofovir disoproxil fumarate; VL: viral load; XTC: emtricitabine or lamivudine.

Outcome	Overall N=2321	AZT/XTC/LPV/r N=915	AZT/XTC/DTG N=415	TDF/XTC/DTG N=991
Retention outcomes, n (%)				
Death or LTFU	720 (31%)	283 (31%)	117 (28%)	320 (32%)
Death	29 (1%)	3 (0%)	9 (2%)	17 (2%)
LTFU	691 (30%)	280 (31%)	108 (26%)	303 (31%)
Days to death or LTFU, median (IQR)	317 (126, 508)	310 (115, 525)	342 (189, 524)	293 (111, 482)
Transfer-out[a]	126 (5%)	52 (6%)	22 (5%)	52 (5%)
Days to transfer-out, median (IQR)	291 (141, 513)	316 (153, 556)	420 (146, 528)	197 (140, 276)
In care without 24-month VL	205 (9%)	59 (6%)	36 (9%)	110 (11%)
In care with 24-month VL	1270 (55%)	521 (57%)	240 (58%)	509 (51%)
Days to VL result, median (IQR)	727 (668, 787)	731 (679, 795)	721 (668, 780)	722 (653, 783)
Regimen change, n (%)	442 (19%)	200 (22%)	95 (23%)	147 (15%)
Days to regimen change, median (IQR)	251 (111, 497)	376 (156, 555)	251 (126, 474)	182 (84, 337)
VL outcomes, n (%)[b]	N=1270	N=521	N=240	N=509
≤50 copies/mL	739 (58%)	272 (52%)	146 (61%)	321 (63%)
51-999 copies/mL	273 (21%)	107 (21%)	56 (23%)	110 (22%)
≥1000 copies/mL	258 (20%)	142 (27%)	38 (16%)	78 (15%)

[a]16 thereof (8 initially switched to AZT/XTC/LPV/r, 4 to AZT/XTC/DTG, and 4 to TDF/XTC/DTG) transferred out after a regimen change.
[b]Among those who remained in care with a 24-month VL result.

Table 6. Co-primary endpoints and sensitivity analyses. aRD: adjusted risk difference; AZT: zidovudine; CI: confidence interval; DTG: dolutegravir; LTFU: loss to follow-up; TDF: tenofovir disoproxil fumarate; VL: viral load; XTC: emtricitabine or lamivudine.

Outcome	AZT/XTC/LPV/r	AZT/XTC/DTG	TDF/XTC/DTG	aRD, AZT/XTC/DTG - AZT/XTC/LPV/r	aRD, TDF/XTC/DTG - AZT/XTC/LPV/r	aRD, TDF/XTC/DTG - AZT/XTC/DTG
Co-primary endpoints, intention-to-treat analyses, % (95% CI)						
Standardised risk of death or LTFU	31% (27%, 34%)	30% (24%, 35%)	34% (31%, 37%)	-1% (-8%, 5%)	3% (-2%, 8%)	4% (-2%, 11%)
Standardised risk of viraemia >50 copies/mL[2]	49% (45%, 54%)	39% (31%, 46%)	38% (33%, 43%)	-11% (-17%, -4%)	-11% (-17%, -4%)	0% (-10%, 8%)
Co-primary endpoints, per-protocol analyses, % (95% CI)						
Standardised risk of death or LTFU	31% (27%, 34%)	27% (21%, 32%)	34% (31%, 37%)	-4% (-11%, 2%)	3% (-2%, 8%)	7% (1%, 13%)
Standardised risk of viraemia >50 copies/mL	52% (46%, 58%)	38% (29%, 46%)	38% (32%, 42%)	-13% (-25%, -4%)	-14% (-23%, -4%)	-1% (-9%, 9%)

Table 7. Sensitivity analyses. aRD: adjusted risk difference; AZT: zidovudine; CI: confidence interval; DTG: dolutegravir; LTFU: loss to follow-up; TDF: tenofovir disoproxil fumarate; XTC: emtricitabine or lamivudine.

Outcome	AZT/XTC/LPV/r	AZT/XTC/DTG	TDF/XTC/DTG	aRD, AZT/XTC/DTG - AZT/XTC/LPV/r	aRD, TDF/XTC/DTG - AZT/XTC/LPV/r	aRD, TDF/XTC/DTG - AZT/XTC/DTG
Sensitivity analyses, intention-to-treat, % (95% CI)						
Risk of death, LTFU, or transfer-out	36% (32%, 39%)	33% (28%, 39%)	38% (35%, 42%)	-2% (-8%, 5%)	3% (-2%, 8%)	5% (-1%, 12%)
Risk of viraemia >1000 copies/mL[a]	27% (22%, 31%)	16% (11%, 22%)	15% (12%, 18%)	-11% (-18%, -4%)	-12% (-18%, -4%)	-2% (-8%, 5%)
Sensitivity analyses, per-protocol, % (95% CI)						
Risk of death, LTFU, or transfer-out	35% (32%, 39%)	30% (25%, 36%)	38% (35%, 42%)	-5% (-11%, 2%)	3% (-2%, 8%)	8% (1%, 15%)
Risk of viraemia >1000 copies/mL	28% (22%, 33%)	18% (11%, 26%)	14% (11%, 17%)	-10% (-19%, -1%)	-14% (-20%, -7%)	-4% (-13%, 1%)

[a]Among those who remained in care with a 24-month viral load result.

Sensitivity analyses

The standardised risk for the composite outcome of risk of death, LTFU, or transfer-out gave similar results to the co-primary endpoint censoring at transfer-out in both intention-to-treat and per-protocol analysis (Table 7).

Defining viraemia at a threshold of ≥1000 copies/mL, the crude proportion of viraemia among those retained in care with a 24-month viral load result was 142/521 (27%) in the AZT/XTC/LPV/r group, 38/240 (16%) with AZT/XTC/DTG, and 78/509 (15%) with TDF/XTC/DTG (Table 5). In line with the co-primary endpoint of viraemia >50 copies/mL, the standardised risk of viraemia ≥1000 copies/mL was higher with AZT/XTC/LPV/r than with AZT/XTC/DTG or TDF/XTC/DTG and similar between AZT/XTC/DTG and TDF/XTC/DTG in both intention-to-treat and per-protocol analysis (Table 7).

Discussion

In this large cohort study with target trial emulation, we observed differential second-line regimen uptake by gender, similar 24-month risk of death or LTFU with different second-line regimens except for slightly worse retention with TDF/XTC/DTG than AZT/XTC/DTG in per-protocol analysis, and lower 24-month viraemia with AZT/XTC/DTG and TDF/XTC/DTG compared with AZT/XTC/LPV/r.

As we only considered switches from TDF/XTC/EFV, the number of switches declined over time with progressing phase-out of EFV- in favour of DTG-based first-line ART. Within first-line ART, we previously showed that women were less likely than men both to newly initiate DTG- compared with EFV-based first-line ART, and to transition from EFV- to DTG-based first-line ART, in the early stages of the DTG rollout in South Africa.[6] In the present study, the lower probability of women to receive a DTG-based regimen upon treatment switch was driven by the early phase of the DTG rollout and subsequently equalised with updated guidance recommending DTG for all.

Previous randomised trials have compared DTG and LPV/r, or DTG with a backbone containing TDF or AZT, in second-line ART. The DAWNING trial (N=624) assessed 48-week viral suppression to <50 copies/mL among adults randomised to second-line DTG or LPV/r, each alongside an NRTI backbone with at least one fully active NRTI based on genotypic resistance testing. At 84% in the DTG and 70% in the LPV/r group, the trial concluded superiority of DTG.[3] In children and adolescents, the ODYSSEY trial compared first- and second-line DTG-based ART with the respective standard of care. In the second-line group (N=396), the NRTI backbone was designed to include at least one NRTI with preserved activity based on resistance testing or assumed based on treatment history, and the standard of care mostly consisted of LPV/r-based ART. At 96-weeks, viral suppression to <50 copies/mL was achieved by 81% receiving DTG and 72% with the standard of care.[19] Finally, the NADIA trial randomised participants failing first-line ART to either DTG or darunavir as the second-line core agent, and to either recycling tenofovir/lamivudine from first-line ART or changing to AZT/lamivudine as the second-line NRTI backbone. Among those receiving DTG (N=235), 84% with recycled tenofovir/lamivudine versus 77% changing to AZT/lamivudine had 96-week viral suppression to <50 copies/mL, indicating non-inferiority.[5]

Our findings thus largely align with previous findings from randomised trials (although with far higher proportions of viraemia in this routine care cohort) and with a previous assessment of 12-month second-line treatment outcomes in this setting.[7] Our findings are encouraging regarding the continued rollout of DTG and recycling of the TDF/XTC backbone from first-line ART, but also highlight substantial gaps in retention in care and viral suppression. This is of particular concern in light of emergent DTG resistance[8–10] and considering even low-level viraemia below 1000 copies/mL, which here make up more than half of recorded viraemia, is associated with subsequent higher-level viraemia and/or treatment failure.[20–22] Better strategies to improve retention in care and support adherence for people on second-line ART are thus urgently needed.

The strengths of this study include its large sample size, 24-month follow-up, representation of treatment outcomes in routine care, and use of target trial emulation methodology aiming to minimise confounding. However, it also has limitations. First, the study period coincides with the transition from TDF/XTC/EFV to TDF/XTC/DTG in first-line ART. This could disadvantage the TDF/XTC/DTG group in two ways: people taking TDF/XTC/EFV whose viraemia was not appropriately addressed might have changed to TDF/XTC/DTG within the first-line transition without adequate adherence support (we do not have data on provision of enhanced adherence counselling), whereas switches to the other two regimens indicate deliberate clinical action; furthermore, for people with treatment failure who received enhanced adherence counselling while taking TDF/XTC/EFV but had clear adherence challenges, the switch to second-line ART may have been delayed with the aim to address adherence first until they were switched to TDF/XTC/DTG by default with the progressing phasing-out of EFV. These considerations might explain the relatively high point estimate for death or LTFU with TDF/XTC/DTG and make the observed similar retention and superior viral suppression compared with

AZT/XTC/LPV/r all the more reassuring. Second, we were not able to link individuals between healthcare facilities but instead relied on Tier. Net patient outcome reporting for transfers and death, and then derived LTFU from unexplained missed clinic visits. This may have led to an overestimation of LTFU and underestimation of death and transfers.[23] Third, while target trial emulation aims to minimise bias, we cannot rule out residual unmeasured confounding.

Overall, our findings suggest similar retention in care and superior viral suppression with DTG-based second-line regimens, compared with AZT/XTC/LPV/r. However, they also highlight the urgent need to improve treatment outcomes of second-line ART. Overall, these findings support the WHO recommendation for preferred use of DTG-based second-line ART.

Ethics and consent

The cohort study within which this work was conducted was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BE646/17; latest approval 13.02.2025), the KwaZulu-Natal Provincial Health Research Ethics Committee (KZ_201807_021; 20.01.2025), the eThekwini Municipality Health Unit (05.03.2024), the uMkhanyakude District Health Office (16.05.2024) and the uMgungundlovu District Health Office (19.02.2025), with a waiver of consent for analysis of de-identified, routinely collected data. This research was conducted in alignment with the Declaration of Helsinki.

Author contributions

JD, NG, and LL conceptualised the study. YS, MK, YS, TK, LH, and TN oversaw data collection. TK and JvdM oversaw data curation. YS, MK, KT, LH, TN, NG, and JD were responsible for various components of project administration. JAB, LL, CB, JvdM, KA, and JD analysed the data. JAB drafted the manuscript. JAB and JD had full access to all data in the study and final responsibility to submit for publication. All authors contributed to interpretation of results, critically reviewed and edited the manuscript, and consented to final publication.

Data availability statement

We cannot publicly share the data used for this analysis because of the legal (Protection of Personal Information Act) and ethical requirements regarding the use of routinely collected clinical data in South Africa, and because our approved study protocol does not include permission to share the data. Interested parties can request access to the data from the KwaZulu-Natal Provincial Department of Health, the eThekwini Municipality Health Unit and the South African National Department of Health TB/HIV Information System (contact details obtainable upon request to JD as the corresponding author). We are not able to specify conditions under which access will be granted, as access must be approved by the appropriate ethics committees.

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References

1. World Health Organization: *Interim Guidelines: Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-Exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV. Supplement to the 2016 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection.* World Health Organization; 2018.
Reference Source

2. World Health Organization: *Policy Brief. Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-Exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV. HIV Treatment - Interim Guidance.* World Health Organization; 2018.
Reference Source

3. Aboud M, Kaplan R, Lombaard J, *et al.*: **Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial.** *Lancet Infect. Dis.* 2019; **19**(3): 253–264.
PubMed Abstract | **Publisher Full Text**

4. Paton NI, Musaazi J, Kityo C, *et al.*: **Dolutegravir or Darunavir in Combination with Zidovudine or Tenofovir to Treat HIV.** *N. Engl. J. Med.* 2021; **385**(4): 330–341.
Publisher Full Text

5. Paton NI, Musaazi J, Kityo C, *et al.*: **Efficacy and safety of dolutegravir or darunavir in combination with lamivudine plus either zidovudine or tenofovir for second-line treatment of HIV infection (NADIA): week 96 results from a prospective, multicentre, open-label, factorial, randomised, non-inferiority trial.** *Lancet HIV.* 2022; **9**(6): e381–e393.
Publisher Full Text

6. Dorward J, Sookrajh Y, Khubone T, *et al.*: **Implementation and outcomes of dolutegravir-based first-line antiretroviral therapy for people with HIV in South Africa: a retrospective cohort study.** *Lancet HIV.* 2023; **10**(5): e284–e294.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

7. Asare K, Sookrajh Y, van der Molen J, *et al.*: **Clinical outcomes with second-line dolutegravir in people with virological failure on first-line non-nucleoside reverse transcriptase inhibitor-based regimens in South Africa: a retrospective cohort study.**

Lancet Glob. Health. 2024; **12**(2): e282–e291.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

8. Loosli T, Hossmann S, Ingle SM, *et al.*: **HIV-1 drug resistance in people on dolutegravir-based antiretroviral therapy: a collaborative cohort analysis.** *Lancet HIV.* 2023; **10**: e733–e741.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

9. Tschumi N, Lukau B, Tlali K, *et al.*: **Emergence of acquired dolutegravir resistance in treatment-experienced people with HIV in Lesotho.** *Clin. Infect. Dis.* 2024; **79**(5): 1208–1222.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

10. Skrivankova VW, Huwa J, Muula G, *et al.*: **Virologic Failure and Drug Resistance After Programmatic Switching to Dolutegravir-based First-line Antiretroviral Therapy in Malawi and Zambia.** *Clin. Infect. Dis.* June 7, 2024; **80**: 120–128.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

11. Hansford HJ, Cashin AG, Jones MD, *et al.*: **Reporting of Observational Studies Explicitly Aiming to Emulate Randomized Trials: A Systematic Review.** *JAMA Netw. Open.* 2023; **6**(9): e2336023.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

12. Hernán MA, Robins JM: **Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available.** *Am. J. Epidemiol.* 2016; **183**(8): 758–764.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

13. von Elm E, Altman DG, Egger M, *et al.*: **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *Lancet.* 2007; **370**(9596): 1453–1457.
Publisher Full Text

14. Simon-Tillaux N, Martin GL, Hajage D, *et al.*: **Conducting observational analyses with the target trial emulation approach: a methodological systematic review.** *BMJ Open.* 2024; **14**(11): e086595.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

15. Hansford HJ, Cashin AG, Jones MD, *et al.*: **Development of the TrAnsparent ReportinG of observational studies Emulating a Target trial (TARGET) guideline.** *BMJ Open.* 2023; **13**(9): e074626.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

16. Zuo H, Yu L, Campbell SM, *et al.*: **The implementation of target trial emulation for causal inference: a scoping review.** *J. Clin. Epidemiol.* 2023; **162**: 29–37.
PubMed Abstract | **Publisher Full Text**

17. 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**(1): 18908.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

18. Cole SR, Hernán MA: **Constructing inverse probability weights for marginal structural models.** *Am. J. Epidemiol.* 2008; **168**(6): 656–664.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

19. Turkova A, White E, Mujuru HA, *et al.*: **Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children.** *N. Engl. J. Med.* 2021; **385**(27): 2531–2543.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

20. Bareng OT, Moyo S, Mudanga M, *et al.*: **Low-Level Viremia among Adults Living with HIV on Dolutegravir-Based First-Line Antiretroviral Therapy Is a Predictor of Virological Failure in Botswana.** *Viruses.* 2024; **16**(5): 720.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

21. Kohler M, Brown JA, Tschumi N, *et al.*: **Clinical Relevance of Human Immunodeficiency Virus Low-level Viremia in the Dolutegravir era: Data From the Viral Load Cohort North-East Lesotho (VICONEL).** *Open Forum Infect. Dis.* 2024; **11**(2): ofae013.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

22. Sodeke O, Milligan K, Ezeuko I, *et al.*: **Longitudinal viral load outcomes of adults with HIV after detectable viremia on tenofovir, lamivudine, and dolutegravir.** *AIDS.* 2024; **38**(11): 1714–1719.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**

23. Etoori D, Wringe A, Kabudula CW, *et al.*: **Misreporting of Patient Outcomes in the South African National HIV Treatment Database: Consequences for Programme Planning, Monitoring, and Evaluation.** *Front. Public Health.* 2020; **8**: 100.
PubMed Abstract | **Publisher Full Text** | **Free Full Text**