Implementation and outcomes of dolutegravir-based first-line antiretroviral therapy for people with HIV in South Africa: a retrospective cohort study

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See Comment page e274

For the isiZulu translation of the abstract see Online for appendix 1

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Summary

Background There are few data assessing the uptake of first-line dolutegravir among men and women living with HIV in low-income and middle-income countries, and subsequent clinical outcomes in non-trial settings. We aimed to determine dolutegravir uptake in women, and the effect of dolutegravir on clinical outcomes in routine care in South Africa.

Methods In this cohort study, we analysed deidentified data from adults receiving first-line antiretroviral therapy (ART) at 59 South African clinics from Dec 1, 2019, to Feb 28, 2022, using two distinct cohorts. In the initiator cohort, we used Poisson regression models to assess the outcome of initiation with dolutegravir-based ART by gender, and associations between dolutegravir use and the outcomes of 12-month retention in care and viral suppression at less than 50 copies per mL. In the transition cohort, comprising adults who received non-dolutegravir-based first-line ART in December, 2019, we used Cox proportional hazards models to assess the outcome of transition to first-line dolutegravir by gender. We then used time-dependent propensity score matching to compare the outcomes of subsequent 12-month retention in care and viral suppression between people who transitioned to dolutegravir and those who had not yet transitioned at the same timepoint. In both the initiation and transition cohort, the primary viral load analysis was an intention-to-treat analysis, with a secondary as-treated analysis that excluded people who changed their ART regimen after baseline.

Findings In the initiator cohort, between Dec 1, 2019, and Feb 28, 2022, 45 392 people were initiated on ART. 23 945 (52·8%) of 45 392 were non-pregnant women, 4780 (10·5%) were pregnant women, and 16 667 (36·7%) were men. The median participant age was 31·0 years (IQR 26·0–38·0) and 2401 (5·3%) were receiving tuberculosis treatment at time of ART initiation. 31 264 (68·9%) of 45 392 people were initiated on dolutegravir, 14 102 (31·1%) on efavirenz, and 26 (0·1%) on nevirapine. In a univariable Poisson regression model, pregnant women (risk ratio [RR] 0·57, 95% CI 0·49 to 0·66; risk difference –35·4%, 95% CI –42·3 to –28·5) and non-pregnant women (RR 0·78, 0·74 to 0·82; risk difference –18·4%, –21·6 to –15·2) were less likely to be initiated on dolutegravir than were men. In Poisson models adjusted for age, gender (including pregnancy), time, tuberculosis status, and initiation CD4 count, people initiated on dolutegravir were more likely to be retained in care at 12 months (adjusted RR 1·09, 95% CI 1·04 to 1·14; adjusted risk difference 5·2%, 2·2 to 8·4) and virally suppressed (adjusted RR 1·04, 95% CI 1·01 to 1·06; adjusted risk difference 3·1%, 1·2 to 5·1) compared with those initiated on non-dolutegravir-based regimens. For the transition cohort, on Dec 1, 2019, 180 956 people were receiving non-dolutegravir-based first-line ART at the study clinics, of whom 124 168 (68·6%) were women. The median age was 38 years (IQR 32–45), and the median time on ART was 3·9 years (2·0–6·4) years, with most people receiving efavirenz (178 624 [98·7%] people) and tenofovir (178 148 [98·4%]). By Feb 28, 2022, 121 174 (67·0%) of 180 956 people had transitioned to first-line dolutegravir at a median of 283 days (IQR 203–526). In a univariable Cox regression model the hazard of being transitioned to dolutegravir was lower in women than in men (hazard ratio 0·56, 95% CI 0·56 to 0·57). Among 92 318 propensity score matched people, the likelihood of retention in care was higher among the dolutegravir group compared with matched controls (adjusted RR 1·03, 95% CI 1·02 to 1·03; risk difference 2·5%, 95% CI 2·1 to 2·9). In the dolutegravir group, 33 423 (90·5%) of 36 920 people were suppressed at less than 50 copies per mL compared with 31 648 (89·7%) of 35 299 matched controls (adjusted RR 1·01, 95% CI 1·00 to 1·02; risk difference 0·8%, 95% CI 0·3 to 1·4).

Interpretation Women were less likely to receive dolutegravir than men. As dolutegravir was associated with improved outcomes, roll-out should continue, with a particular emphasis on inclusion of women.

Funding Wellcome Trust, Africa Oxford Initiative, International Association of Providers of AIDS Care, and Bill & Melinda Gates Foundation.

Research in context

Evidence before this study

We searched PubMed from database inception to Oct 5, 2022, with no language restrictions, with the terms [dolutegravir AND (rollout OR implementation OR outcomes) AND Africa] and identified additional studies using hand searches of reference lists and cited papers. After concerns were raised in 2018 regarding a potential association between dolutegravir use at conception and neural tube defects, there have been three observational studies to compare the uptake of dolutegravir between women and men in Africa. Two studies early in the roll-out of dolutegravir in low-income and middle-income countries found that around 60% of men compared with 30% of women had been transitioned to dolutegravir, and a smaller study from four African countries found that by September, 2021, 68% of women had been transitioned to dolutegravir, compared with 80% of men. Regarding clinical outcomes on dolutegravir, a large network meta-analysis of 68 randomised trials (four of which directly compared dolutegravir 50 mg daily with efavirenz among people newly initiating first-line antiretroviral therapy [ART]) found that dolutegravir had better viral suppression, less HIV drug resistance, and fewer discontinuations compared with first-line efavirenz. To our knowledge, no trials have assessed transition to dolutegravir among people already receiving efavirenz. Despite the large scale dolutegravir roll-out in low-income and middle-income countries (LMICs), there have been few assessments of the effectiveness of dolutegravir compared with other first-line regimens in non-trial settings. Among people initiating first-line ART in Brazil, 12-month viral suppression with less than 50 copies per mL was higher among people initiated on dolutegravir versus efavirenz, but people with no 12-month viral load were excluded from the study and loss-to-follow-up was not assessed. A retrospective cohort study among 3108 people in four African countries found a higher hazard of viraemia greater than 1000 copies per mL among people who remained on non-dolutegravir regimens compared with those who transitioned to dolutegravir. However, this analysis was susceptible to multiple biases, including systematic differences in viral load schedules and the start of follow-up time between the two groups, and the use of events after baseline to determine inclusion in the time-to-event analysis. Regarding the use of dolutegravir among people with tuberculosis, rifampicin has been found to reduce dolutegravir concentrations. This effect can be overcome by doubling the dose of dolutegravir to 50 mg twice daily, an approach that was found to be well tolerated in the INSPIRING trial. In non-trial settings, a cohort study among 3563 people with HIV receiving rifampicin-containing tuberculosis treatment found that those on dolutegravir-based regimens had better viral suppression compared with those who received efavirenz.

Added value of this study

To our knowledge, we present the results of the largest study to date to assess dolutegravir uptake in women versus men and to compare outcomes with non-dolutegravir first-line regimens in routine care settings. We found that younger women were less likely to be initiated or transitioned to dolutegravir early in the roll-out, but this difference resolved once South African guidelines recommended dolutegravir for all people living with HIV, irrespective of child-bearing potential. Among people initiating first-line ART or already receiving first-line ART, dolutegravir use was associated with better 12-month retention and viral suppression. The association between dolutegravir and better viral suppression was even higher among people being treated for tuberculosis.

Implications of all the available evidence

Taken together, these findings support the ongoing roll-out of dolutegravir for first-line ART in LMICs, including among people being treated for tuberculosis. Our findings also suggest that, because of initial safety concerns, women have been excluded from receiving an effective ART regimen. Therefore, efforts should be made to ensure that women who previously did not receive dolutegravir are now offered dolutegravir alongside updated evidence regarding safety and effectiveness. Further evidence from routine care settings regarding adverse events, in particular weight gain, is needed.

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See **Online** for appendix 2

Introduction

Since 2018, WHO has recommended dolutegravir-based first-line antiretroviral therapy (ART)[1] because of clinical trial evidence of increased efficacy compared with non-nucleoside reverse transcriptase inhibitors. This increased efficacy is largely driven by improved tolerability and fewer discontinuations, and dolutegravir is also robust against the development of HIV drug resistance.[2,3] Initially, safety concerns regarding a potential increased risk of neural tube defects if dolutegravir was taken at conception led WHO to recommend restricted use among women of child-bearing potential.[1] However, new data suggesting a lower risk of neural tube defects than previously thought, risk–benefit analyses from modelling studies,[4] and community advocacy[5] led WHO to remove these restrictions in July, 2019.[1] By mid-2022, dolutegravir had been introduced into the preferred first-line ART regimen in around 108 countries.[6]

To date, there are few published studies that examine the effect of the previous restrictions on dolutegravir uptake over time,[7–9] and few data comparing the effectiveness of dolutegravir with alternative first-line regimens in non-trial settings in Africa.[10] In regions with a high prevalence of tuberculosis co-infection, there are also important concerns regarding the use of dolutegravir with rifampicin-containing tuberculosis treatment, which reduces dolutegravir drug concentrations. This issue can be overcome by doubling the dolutegravir dose,[11] which might not always be feasible in large-scale ART programmes. Dolutegravir use is particularly pertinent in South Africa,

where there are over 7·5 million people living with HIV, the majority of whom are women of child-bearing potential, and tuberculosis incidence is high.

In this study, we aimed to assess the effect of the first-line dolutegravir roll-out on HIV treatment outcomes in South Africa. We determined the extent to which women were less likely to receive dolutegravir over time, the relationship between dolutegravir use and retention in care and viral suppression, and the effect of dolutegravir use on HIV treatment outcomes among people receiving concurrent tuberculosis treatment.

See Online for appendix 2

Methods

Study design and participants

We did a cohort study using deidentified, routinely collected data from 59 public sector, primary care clinics run by the eThekwini Municipality Health Unit, in the province of KwaZulu-Natal, South Africa. ART is provided free of charge in accordance with South African National Department of Health guidelines,[12] which recommended dolutegravir from Dec 1, 2019. Initially, ART initiations were prioritised, and women of child-bearing potential were required to sign an acknowledgement of risk form. On Feb 24, 2020, eligibility was expanded to include people already receiving first-line ART, with a risk–benefit discussion replacing the signed risk form for women of child-bearing potential.[13] In June, 2021, the risk–benefit discussion for women was removed, and dolutegravir became the preferred first-line ART regimen.[14] For people living with tuberculosis co-infection, dolutegravir was only recommended after completing tuberculosis treatment. Viral load testing was recommended annually, and transition to first-line dolutegravir was only recommended if people had a suppressed viral load of less than 50 copies per mL in the previous 6 months, or consecutive viral loads between 50 and 999 copies per mL.[12]

For more on the **South African National Department of Health's TB/HIV Information Systems** see https://www.tbhivinfosys.org.za/

We analysed two mutually exclusive groups: the initiator cohort and the transition cohort. For the initiator cohort, we evaluated dolutegravir use by gender among all people living with HIV aged 15 years and older and newly initiating first-line ART (irrespective of nucleoside reverse transcriptase inhibitor backbone) at participating clinics, between Dec 1, 2019, and Feb 28, 2022. We excluded people with known previous ART exposure, as South African guidelines recommend reinitiating the previous regimen, which would often not be dolutegravir-based. We then analysed outcomes among those who initiated ART before Dec 1, 2020, and therefore had at least 12 months of follow-up time plus 90 days to assess retention in care before the data cutoff on Feb 28, 2022. We assessed viral load outcomes only among those who were retained in care at 12 months.

For the transition cohort, we assessed transition to first-line dolutegravir by gender among people living with HIV aged 15 years and older who were in care and receiving non-dolutegravir first-line ART at participating clinics on Dec 1, 2019. We excluded those with a viral load of 1000 copies per mL or greater in the previous 12 months, as they would not have been eligible for transition to first-line dolutegravir. We then analysed outcomes among a subset who had initiated dolutegravir before Dec 1, 2020, compared with people who had not initiated dolutegravir at the same timepoint, matched 1:1 using propensity score matching (appendix 2 pp 1–2).

This work was approved by the University of Kwazulu-Natal Biomedical Research Ethics Committee (BE646/17), the KwaZulu-Natal Provincial Health Research Ethics Committee (KZ_201807_021), the THIS Data Request Committee, and the eThekwini Municipality Health Unit, with a waiver for informed consent for analysis of deidentified, routinely collected data.

Data sources and variables

For patients initiating and receiving ART in the South African public sector, data on demographics, clinical status, ART, and clinic visits are routinely recorded in the TIER.net[15] electronic register. TIER.net data from participating clinics were collated and deidentified by the South African National Department of Health's TB/HIV Information Systems before being extracted for analysis. We used demographic and clinical variables recorded at ART initiation or during follow-up.

Outcomes

We assessed the main outcomes of first-line dolutegravir use, 12-month retention in care and 12-month viral suppression. We defined first-line dolutegravir use from the ART initiation regimen (initiator cohort) or the date of first use of dolutegravir in a first-line regimen (transition cohort; see appendix 2 p 1 for full definition). We defined retention in care as not being recorded in TIER.net as deceased, lost to follow-up (defined as 90 days late for a visit by the South African ART programme, with date of last visit used as date of loss to follow-up), or transferred out to another clinic (as we could not access or link to data at other clinics to establish retention in care). We defined viral suppression as less than 50 copies per mL, as per clinical trials[16–18] and South African guidelines. In this programmatic setting, not all patients had annual viral loads available. Therefore, in both cohorts we included viral loads 5–18 months after baseline, and used the result closest to 12 months.

Statistical analysis

Among the initiator cohort, we first used univariable Poisson regression models with robust SEs to estimate relative risks for the association between gender and the outcome of dolutegravir initiation. We also did sensitivity analyses, defined a priori, to assess whether the effect of gender on dolutegravir use was modified by age at ART initiation and by time. We then used univariable and multivariable Poisson regression models with robust SEs to assess the association between being initiated on dolutegravir and 12-month retention in care and viral

suppression. To assess whether tuberculosis treatment had an effect on viral suppression with dolutegravir, we did sensitivity analyses, defined a priori, with an interaction term between dolutegravir use and tuberculosis status.

Among the transition cohort, we used univariable Cox proportional hazards models to assess the association between gender and time to transition to a dolutegravir-based first-line regimen. We started follow-up time from Dec 1, 2019, and censored people at date of loss-to-follow-up, death, transfer to another clinic, or switch to second-line ART. We also censored people with a viral load greater than or equal to 1000 copies per mL during follow-up, as they would not have been eligible for immediate transition to first-line dolutegravir.

Comparing outcomes between people transitioned and not transitioned to dolutegravir is complicated by the lack of a clear baseline time in those whose treatment remains unchanged, and potential underlying differences between the two groups. We addressed these issues by emulating a target trial, in which each person who transitioned to dolutegravir was matched to a control who had not yet been transitioned at the same timepoint.[19] To increase comparability between the two groups, we matched participants 1:1 using a time-dependent propensity score of the log-hazard of transition to dolutegravir,[20,21] with

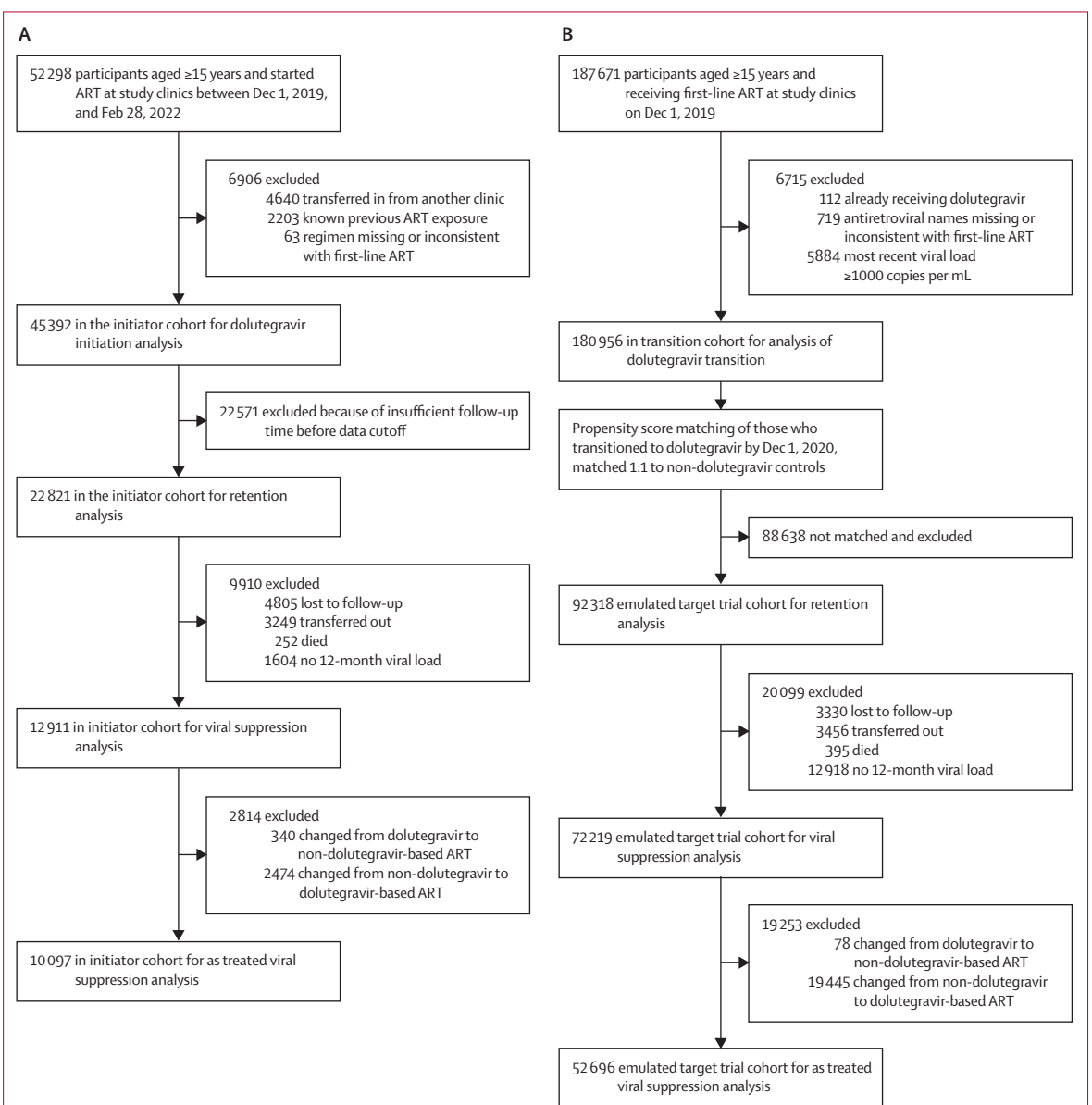

Figure 1: **Flow diagram of the initiation cohort (A) and transition cohort (B) at 59 primary care clinics in South Africa**
ART=antiretroviral therapy.

	Total (n=45 392)	Non-dolutegravir regimen (n=14 128)	Dolutegravir regimen (n=31 264)	Risk ratio (95% CI)
Gender				
Male	16 667 (36·7%)	2948 (17·7%)	13 719 (82·3%)	1 (ref)
Female, not pregnant	23 956 (52·8%)	8650 (36·1%)	15 306 (63·9%)	0·78 (0·74–0·82)
Female, pregnant	4769 (10·5%)	2530 (53·1%)	2239 (46·9%)	0·57 (0·49–0·66)
Age, years				
≥55	1170 (2·6%)	277 (23·7%)	893 (76·3%)	1 (ref)
45–54	3823 (8·4%)	862 (22·5%)	2961 (77·5%)	1·01 (0·98–1·05)
35–44	11 833 (26·1%)	3127 (26·4%)	8706 (73·6%)	0·96 (0·93–1·00)
25–34	20 274 (44·7%)	6690 (33·0%)	13 584 (67·0%)	0·88 (0·84–0·92)
15–24	8292 (18·3%)	3172 (26·4%)	5120 (61·7%)	0·81 (0·76–0·86)
Initiation time period				
December, 2019, to February, 2020	7174 (15·8%)	5797 (80·8%)	1377 (19·2%)	1 (ref)
March to May, 2020	5582 (12·3%)	2953 (52·9%)	2629 (47·1%)	2·45 (2·03–2·96)
June to August, 2020	4940 (10·9%)	1730 (35·0%)	3210 (65·0%)	3·39 (2·74–4·19)
September to November, 2020	5125 (11·3%)	1473 (28·7%)	3652 (71·3%)	3·71 (2·99–4·60)
December, 2020, to February, 2021	4663 (10·3%)	936 (20·1%)	3727 (79·9%)	4·16 (3·34–5·20)
March to May, 2021	5668 (12·5%)	602 (10·6%)	5066 (89·4%)	4·66 (3·72–5·83)
June to August, 2021	4216 (9·3%)	321 (7·6%)	3895 (92·4%)	4·81 (3·85–6·02)
September to November, 2021	4063 (9·0%)	180 (4·4%)	3883 (95·6%)	4·98 (3·97–6·24)
December, 2021, to February, 2022	3961 (8·7%)	136 (3·4%)	3825 (96·6%)	5·03 (4·03–6·28)
Tuberculosis at ART initiation				
No tuberculosis	42 991 (94·7%)	13 032 (30·3%)	29 959 (69·7%)	1 (ref)
Known tuberculosis	2401 (5·3%)	1096 (45·6%)	1305 (54·4%)	0·78 (0·70–0·87)
Initiation CD4 count (cells per µL)				
<200	7038 (15·5%)	2090 (29·7%)	4948 (70·3%)	1 (ref)
200–349	7543 (16·6%)	2381 (31·6%)	5162 (68·4%)	0·97 (0·95–1·00)
350–499	6704 (14·8%)	2187 (32·6%)	4517 (67·4%)	0·96 (0·93–0·98)
≥500	11 020 (24·3%)	3670 (33·3%)	7350 (66·7%)	0·95 (0·92–0·98)
Missing	13 087 (28·8%)	3800 (29·0%)	9287 (71·0%)	1·01 (0·94–1·09)

Data are n (%). Percentages in the left-hand column were calculated with the total in the header as the denominator. All other percentages used the row total as the denominator. ART=antiretroviral therapy.

Table 1: **Univariable Poisson regression models of baseline characteristics associated with being initiated on dolutegravir-based first-line ART versus non-dolutegravir ART**

direct matching by time since most recent viral load, and whether the participant was in a differentiated ART delivery programme. Individuals could only be matched once, and we only matched participants who transitioned to dolutegravir before Dec 1, 2020, to allow 12 months of follow-up time. Further details are provided in appendix 2 (pp 1–2). We then used multivariable Poisson regression models to compare the outcomes of 12-month retention in care and viral suppression between people who transitioned to dolutegravir and their matched controls.

In both the initiation and transition cohort, the primary viral load analysis was an intention-to-treat analysis, with a secondary as-treated analysis that excluded people who changed their ART regimen after baseline. Dolutegravir roll-out and clinical outcomes might have varied by clinic and we accounted for this using robust SEs. We did not adjust for multiple comparisons. We present both risk ratios (RRs) and risk differences to show the relative strength of an association and the absolute difference. We included a specific category for missing baseline CD4 cell count data.

We analysed data using R 4.2.0 and STATA 14.0.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

In the initiator cohort, between Dec 1, 2019, and Feb 28, 2022, 45 392 people were initiated on ART (figure 1A). 23 945 (52·8%) of 45 392 were non-pregnant women, 4780 (10·5%) were pregnant women, and 16 667 (36·7%) were men (table 1). The median participant age was 31·0 years (IQR 26·0–38·0) and 2401 (5·3%) were receiving tuberculosis treatment at time of ART initiation.

31 264 (68·9%) of 45 392 people were initiated on dolutegravir, 14 102 (31·1%) on efavirenz, and 26 (0·1%) on nevirapine. Dolutegravir use increased over time; between Dec 1, 2019, and Feb 29, 2020, 1377 (19·2%) of 7174 participants were initiated on dolutegravir-based ART, compared with 3825 (96·6%) of 3961 participants between Dec 1, 2021, and Feb 28, 2022 (table 1). Over the study period, 2239 (46·9%) of 4769 pregnant women, 15 306 (63·9%) of 23 956 non-pregnant women, and 13 719 (82·3%) of 16 667 men were initiated on dolutegravir. In a univariable Poisson regression model, pregnant women (RR 0·57, 95% CI 0·49 to 0·66; risk difference –35·4%, 95% CI –42·3 to –28·5) and non-pregnant women (RR 0·78, 0·74 to 0·82; risk difference –18·4%, –21·6 to –15·2) were less likely to be initiated on dolutegravir than were men (table 1).

The effect of gender was strongest among people aged 15–24 years (non-pregnant women *vs* men RR 0·73, 95% CI 0·69–0·77), and decreased with older age, with no difference between men and women in the 55 years and older group (RR 0·97, 0·90–1·03; Wald test for interaction p<0·0001; appendix 2 p 2). Early in the dolutegravir roll-out, women were much less likely to receive dolutegravir than were men (Dec 1, 2019, to Feb 29, 2020: non-pregnant women RR 0·29, 95% CI 0·23–0·38, pregnant women 0·25, 0·12–0·53, compared with men; appendix 2 p 2), but this difference declined and had disappeared by Sept 1, 2021, to Nov 30, 2021, for both non-pregnant (RR 1·00, 95% CI 0·98–1·03) and pregnant women (0·98, 0·94–1·02; Wald test for interaction p<0·0001).

22 821 people initiated ART before Dec 1, 2020, and had the opportunity to complete 12 months of follow-up, plus 90 days to assess retention, before the data cutoff. 476 (4·4%) of 10 868 people who were initiated on

a dolutegravir-based regimen were changed to efavirenz (n=462) or another non-dolutegravir-based regimen (n=14), after a median of 120 days (IQR 66–201) from ART initiation. 2944 (24·6%) of 11 953 people initiated on a non-dolutegravir regimen were changed to dolutegravir, after a median of 191 days (IQR 98–252).

By 12 months, in the dolutegravir group 7108 (65·4%) of 10 868 people were retained in care, 1391 (12·8%) had transferred to another clinic, 2233 (20·5%) were lost to follow-up, and 136 (1·3%) were known to have died, compared with 7407 (62·0%) of 11 953 people in the non-dolutegravir group retained in care, 1858 (15·5%) transferred to another clinic, 2572 (21·5%) lost to follow-up, and 116 (1·0%) who had died. Overall median time to loss to follow-up was 35 days (IQR 0–156); 1895 (39·4%) of the 4905 people who were lost to follow-up were not seen again after ART initiation. In a Poisson model adjusted for age, gender (including pregnancy), time, tuberculosis status, and initiation CD4 cell count, people initiated on dolutegravir were more likely to be retained in care compared with those initiated on non-dolutegravir-based regimens (adjusted RR 1·09, 95% CI 1·04 to 1·14; adjusted risk difference 5·2%, 2·2 to 8·4; table 2). In post-hoc sensitivity analysis that included transfers to another clinic as retained in care, the association between dolutegravir and retention was attenuated (adjusted RR 1·03, 95% CI 0·99 to 1·08; adjusted risk difference 2·4%, 95% CI –0·9 to 5·7).

12 911 (88·9%) of 14 515 people retained in care at 12 months had a documented viral load result after a median of 365 days (IQR 347–380) from initiation. Of these, 10 616 (82·2%) of 12 911 responses were supressed, at less than 50 copies per mL. In a multivariable model adjusted for the same variables as the retention model, people initiated on dolutegravir had better viral suppression than did those on non-dolutegravir regimens (adjusted RR 1·04, 95% CI 1·01–1·06; adjusted risk difference 3·1%, 1·2–5·1; table 3). The association between dolutegravir use and viral suppression was even stronger in as-treated analyses, which excluded people who had a change in ART from or to dolutegravir after ART initiation (adjusted RR 1·09, 95% CI 1·05–1·12; adjusted risk difference 6·8%, 95% CI 4·3–9·4; appendix 2 p 3).

316 (40·8%) of 774 people with tuberculosis were initiated on dolutegravir. In this group, the association between dolutegravir and viral suppression was stronger (adjusted RR 1·14, 95% CI 1·07–1·22) than among those without tuberculosis (1·03, 1·01–1·06; Wald test for interaction p=0·0057; appendix 2 p 3).

For the transition cohort, on Dec 1, 2019, 180 956 people were receiving non-dolutegravir-based first-line ART at the study clinics (figure 1B), of whom 124 168 (68·6%) were women (table 4). The median age was 38 years (IQR 32–45), and the median time on ART was 3·9 years (2·0–6·4), with most people receiving efavirenz (178 624 [98·7%] people) and tenofovir (178 148 [98·4%] people).

Participants were followed up to the endpoint or censoring date for a median of 319 days (IQR 205–646), totalling 206 050 person-years at risk. By Feb 28, 2022, 121 174 (67·0%) of 180 956 people had transitioned to first-line dolutegravir at a median of 283 days (IQR 203–526). 27 702 (15·3%) people were retained in care and continued receiving non-dolutegravir-based first-line ART. 9404 (5·2%) of 180 956 people had a viral load of 1000 copies per mL or greater, 657 (0·4%) had been switched to second-line ART, 12 074 (6·7%) transferred care to another clinic, 9127 (5·0%) were lost to follow-up, and 818 (0·5%) were known to have died. The rate of dolutegravir transition peaked between June 1, 2020, and Aug 31, 2020 (1118·6, 95% CI 1107·0 to 1130·4 per 1000 person-years), and was lowest between Dec 1, 2020, and Feb 28, 2021 (345·3, 337·1–353·7 per 1000 person-years; appendix 2 p 3; figure 2).

In a univariable Cox regression model the hazard of being transitioned to dolutegravir was lower in women

	Retained in care	RR (95% CI)	Adjusted RR* (95% CI)
ART regimen			
Non-dolutegravir regimen	7407/11 953 (62·0%)	1 (ref)	1 (ref)
Dolutegravir regimen	7108/10 868 (65·4%)	1·06 (1·02–1·10)	1·09 (1·04–1·14)
Gender			
Male	5432/8337 (65·2%)	1 (ref)	1 (ref)
Female, not pregnant	7518/11 985 (62·7%)	0·96 (0·94–0·99)	1·04 (1·02–1·07)
Female, pregnant	1565/2499 (62·6%)	0·96 (0·91–1·02)	1·10 (1·02–1·18)
Age, years			
≥55	415/599 (69·3%)	1 (ref)	1 (ref)
45–54	1368/1872 (73·1%)	1·05 (1·00–1·11)	1·05 (0·99–1·11)
35–44	3945/5767 (68·4%)	0·99 (0·94–1·04)	0·99 (0·94–1·04)
25–34	6461/10 377 (62·3%)	0·90 (0·86–0·94)	0·91 (0·86–0·95)
15–24	2326/4206 (55·3%)	0·80 (0·75–0·85)	0·81 (0·76–0·86)
Initiation time period			
December, 2019, to February, 2020	4624/7174 (64·5%)	1 (ref)	1 (ref)
March to May, 2020	3637/5582 (65·2%)	1·01 (0·98–1·05)	0·98 (0·95–1·02)
June to August, 2020	3083/4940 (62·4%)	0·97 (0·93–1·00)	0·94 (0·89–0·99)
September to November, 2020	3171/5125 (61·9%)	0·96 (0·92–1·00)	0·93 (0·88–0·98)
Tuberculosis at ART initiation			
No tuberculosis	13 646/21 660 (63·0%)	1 (ref)	1 (ref)
Known tuberculosis	869/1161 (74·8%)	1·19 (1·14–1·23)	1·17 (1·13–1·22)
Initiation CD4 count (cells per μL)			
<200	2645/3709 (71·3%)	1	1
200–349	2724/3979 (68·5%)	0·96 (0·93–0·99)	0·99 (0·96–1·03)
350–499	2291/3459 (66·2%)	0·93 (0·90–0·96)	0·98 (0·94–1·01)
≥500	3539/5523 (64·1%)	0·90 (0·87–0·93)	0·95 (0·91–0·98)
Missing	3316/6151 (53·9%)	0·76 (0·69–0·83)	0·78 (0·72–0·86)

Data are n/N (%), unless otherwise indicated. Numerators are the number of patients who were retained in care and denominators are the number of patients in each subgroup. ART=antiretroviral therapy. RR=risk ratio. *The primary exposure effect (dolutegravir use) is adjusted for all other variables in the model as potential confounders. Unlike the primary exposure effect, the presented adjusted RRs for potential confounding variables should not be interpreted as the effect of the confounding variable on the outcome.

Table 2: **Univariable and multivariable Poisson regression models of factors associated with retention in care in people initiating dolutegravir and non-dolutegravir-based first-line ART (n=22 821)**

	Viral suppression	RR (95% CI)	Adjusted RR* (95% CI)
ART regimen			
Non-dolutegravir regimen	5327/6541 (81·4%)	1 (ref)	1 (ref)
Dolutegravir regimen	5289/6370 (83·0%)	1·02 (1·00–1·04)	1·04 (1·01–1·06)
Gender			
Male	3808/4796 (79·4%)	1 (ref)	1 (ref)
Female, not pregnant	5685/6771 (84·0%)	1·06 (1·04–1·07)	1·06 (1·04–1·07)
Female, pregnant	1123/1344 (83·6%)	1·05 (1·02–1·08)	1·06 (1·02–1·09)
Age, years			
≥55	319/379 (84·2%)	1 (ref)	1 (ref)
45–54	1036/1248 (83·0%)	0·99 (0·94–1·04)	0·99 (0·94–1·04)
35–44	2902/3556 (81·6%)	0·97 (0·93–1·01)	0·98 (0·93–1·02)
25–34	4707/5708 (82·5%)	0·98 (0·93–1·03)	0·97 (0·92–1·02)
15–24	1652/2020 (81·8%)	0·97 (0·93–1·02)	0·94 (0·90–0·99)
Initiation time period			
December, 2019, to February, 2020	3324/4117 (80·7%)	1 (ref)	1 (ref)
March to May, 2020	2746/3288 (83·5%)	1·03 (1·01–1·06)	1·03 (1·00–1·05)
June to August, 2020	2325/2740 (84·9%)	1·05 (1·03–1·08)	1·03 (1·00–1·06)
September to November, 2020	2221/2766 (80·3%)	0·99 (0·97–1·02)	0·98 (0·95–1·00)
Tuberculosis at ART initiation			
No tuberculosis	10 032/12 137 (82·7%)	1 (ref)	1 (ref)
Known tuberculosis	584/774 (75·5%)	0·91 (0·88–0·95)	0·96 (0·93–1·00)
Initiation CD4 count (cells per µL)			
<200	1786/2426 (73·6%)	1 (ref)	1 (ref)
200–349	2011/2473 (81·3%)	1·10 (1·07–1·14)	1·10 (1·07–1·14)
350–499	1734/2052 (84·5%)	1·15 (1·11–1·19)	1·14 (1·11–1·18)
≥500	2798/3177 (88·1%)	1·20 (1·17–1·23)	1·19 (1·15–1·22)
Missing	2287/2783 (82·2%)	1·12 (1·08–1·15)	1·11 (1·08–1·15)

Data are n/N (%), unless otherwise indicated. Numerators are the number of patients with viral suppression and denominators are the number of patients in each subgroup. ART=antiretroviral therapy. RR=risk ratio. *The primary exposure effect (dolutegravir use) is adjusted for all other variables in the model as potential confounders. Unlike the primary exposure effect, the presented adjusted risk ratios for potential confounding variables should not be interpreted as the effect of the confounding variable on the outcome.

Table 3: **Univariable and multivariable Poisson regression models of factors associated with viral suppression in people initiating dolutegravir and non-dolutegravir-based first-line ART (n=12 911)**

than in men (hazard ratio [HR] 0·56, 95% CI 0·56–0·57; table 4). The effect of gender on dolutegravir transition was largest among younger age groups (15–24 years, HR 0·50, 95% CI 0·46–0·53; ≥55 years, 0·93, 0·90–0·97; appendix 2 p 4; likelihood ratio test for interaction p<0·0001). When including an interaction term between gender and time, the hazard of initiating dolutegravir was lower in women compared with men earlier in the roll-out (Dec 1, 2019, to Feb 29, 2020, HR 0·37, 95% CI 0·34–0·40), but converged as the roll-out progressed, and became higher in women than in men by Sept 1, 2021, to Nov 30, 2021 (1·09, 1·04–1·15; likelihood ratio test for interaction p<0·0001; appendix 2 p 4).

75 223 people had been transitioned to dolutegravir before Dec 1, 2020. After propensity score matching, 46 159 people who transitioned to dolutegravir were matched with 46 159 controls who had not yet been transitioned at the same timepoint, and were included in the target trial. Baseline characteristics were similar between the two groups (appendix 2 p 4). In the dolutegravir group, 88 (0·2%) of 46 159 people subsequently changed back to a non-dolutegravir first-line regimen, at a median of 211 days (IQR 116–308) from baseline. In the matched controls, 23 620 (51·2%) of 46 159 people subsequently transitioned to dolutegravir at a median of 154 days (IQR 73–253) from baseline. By 12 months, 43 178 (93·5%) of 46 159 people in the dolutegravir group were retained in care, 1388 (3·0%) had transferred out, 1460 (3·2%) were lost to follow-up, and 133 (0·3%) were known to have died, compared with 41 959 (90·9%) of 46 159 people retained in care, 2068 (4·5%) transferred, 1870 (4·1%) lost to follow-up, and 262 (0·6%) known to have died in the non-dolutegravir group. The likelihood of retention in care was higher among the dolutegravir group compared with matched controls (adjusted RR 1·03, 95% CI 1·02–1·03; risk difference 2·5%, 95% CI 2·1–2·9), but was partly attenuated in post-hoc sensitivity analysis in which transfers out were included as retained in care (adjusted RR 1·01, 1·00–1·01; risk difference 1·1%, 0·7–1·5). Among those retained in care, 72 219 (84·8%) of 85 137 people had a viral load result after a median of 336 days (IQR 266–422) from baseline. In the dolutegravir group, 33 423 (90·5%) of 36 920 people were suppressed at less than 50 copies per mL compared with 31 648 (89·7%) of 35 299 matched controls (adjusted RR 1·01, 95% CI 1·00–1·02; risk difference 0·8%, 95% CI 0·3–1·4). In sensitivity analysis with an interaction term between dolutegravir use and baseline viral load, dolutegravir was only associated with improved viral suppression among people with baseline viral load of 200 copies per mL or greater (eg, 200–399 copies per mL, adjusted RR 1·15, 95% CI 1·05–1·26; 400–999 copies per mL, 1·25, 1·13–1·38; appendix 2 p 5). In the as-treated analysis, the association between dolutegravir and viral suppression was slightly stronger (adjusted RR 1·03, 95% CI 1·02–1·04; risk difference 2·3%, 95% CI 1·4–3·2; appendix 2 p 5).

Discussion

In this large cohort study at 59 South African clinics, women were less likely to receive dolutegravir than men, with the strongest effect early in the roll-out and among younger women. In people both initiating and already receiving first-line ART, dolutegravir use was associated with better 12-month retention in care and viral suppression. The association between dolutegravir use and viral suppression was stronger among people receiving concurrent tuberculosis treatment when initiating ART, and among people who transitioned to dolutegravir with the most recent viral load at a baseline of 200 copies per mL or greater.

We provide longer-term data compared with studies from earlier in the dolutegravir roll-out, which showed that younger women were initially less likely to receive

	Patients (n=180 956)	Transition to dolutegravir events	Time, person-years	Rate per 100 person-years (95% CI)	Hazard ratio (95% CI)
Gender					
Male	56 788 (31·4%)	41 967	52 094	805·6 (797·9–813·3)	1 (ref)
Female	124 168 (68·6%)	79 207	153 937	514·5 (511·0–518·1)	0·56 (0·56–0·57)
Baseline age category, years					
>55	14 010 (7·7%)	10 075	14 302	704·4 (690·7–718·3)	1 (ref)
45–54	34 223 (18·9%)	25 720	35 322	728·2 (719·3–737·1)	1·04 (1·01–1·06)
35–44	67 118 (37·1%)	46 514	77 154	602·9 (597·4–608·4)	0·82 (0·80–0·84)
25–34	55 944 (30·9%)	33 822	67 823	498·7 (493·4–504·0)	0·66 (0·64–0·67)
15–24	9661 (5·3%)	5043	11 431	441·2 (429·1–453·5)	0·56 (0·54–0·58)
Baseline time on ART, years	3·9 (2·0–6·4)	..	..	..	1·01 (1·01–1·01)
Baseline most recent CD4 count category, cells per µL					
≥500	70 180 (38·8%)	47 141	83 106	567·2 (562·1–572·4)	1 (ref)
350–499	39 875 (22·0%)	27 399	45 353	604·1 (597·0–611·3)	1·10 (1·08–1·11)
200–349	34 093 (18·8%)	23 200	37 544	617·9 (610·0–625·9)	1·14 (1·12–1·15)
<200	21 477 (11·9%)	14 139	22 859	618·5 (608·4–628·8)	1·17 (1·14–1·19)
Missing	15 331 (8·5%)	9295	17 170	541·3 (530·4–552·5)	0·98 (0·96–1·00)
Tuberculosis during follow-up					
No	178 426 (98·6%)	121 008	205 179	589·8 (586·4–593·1)	1 (ref)
Yes	2530 (1·4%)	166	853	194·7 (166·2–226·7)	0·41 (0·35–0·48)
Pregnancy during follow-up					
No	116 628 (64·5%)	120 826	204 581	590·6 (587·3–593·9)	1 (ref)
Yes	7540 (4·2%)	348	1450	239·9 (215·4–266·5)	0·40 (0·36–0·44)
In the Centralised Chronic Medication Dispensing and Distribution programme* during follow-up?					
No	85 523 (47·3%)	79 942	122 844	650·8 (646·3–655·3)	1 (ref)
Yes	95 433 (52·7%)	41 232	83 187	495·7 (490·9–500·5)	0·68 (0·67–0·69)

Data are n (%) or median (IQR), unless otherwise indicated. ART=antiretroviral therapy. *A differentiated ART delivery programme.

Table 4: **Univariable Cox regression models of baseline characteristics associated with transitioning to dolutegravir-based first-line ART**

dolutegravir.[7–9] A multisite study of 134 672 people living with HIV from 11 countries up to March, 2020 (8 months after WHO recommended dolutegravir for all people living with HIV) found that, in people aged 16–49 years, dolutegravir use was lower among women compared with men, but longer-term trends were not assessed.[7] In our study, younger women were less likely to receive dolutegravir up to 2 years after WHO recommended dolutegravir for all. This difference decreased over time and disappeared shortly after South African guidelines recommended dolutegravir for all in June, 2021, with the hazard of transition to dolutegravir becoming higher among women compared with men in the subsequent months, a probable catch-up effect. However, by the end of the follow-up period, women remained less likely overall to be on dolutegravir than men, and 15% of people remained on non-dolutegravir first-line ART.

Retention in care at 12 months was low among people newly initiating ART in our cohort, with a higher proportion transferring to other clinics than reported in a previous study,[22] which might reflect mobility due to COVID-19. Our finding that first-line dolutegravir was associated with better retention in care might be due to increased tolerability, which could be particularly important early in treatment. This finding is similar to results from clinical trials, in which the superior efficacy of dolutegravir has largely been driven by reduced

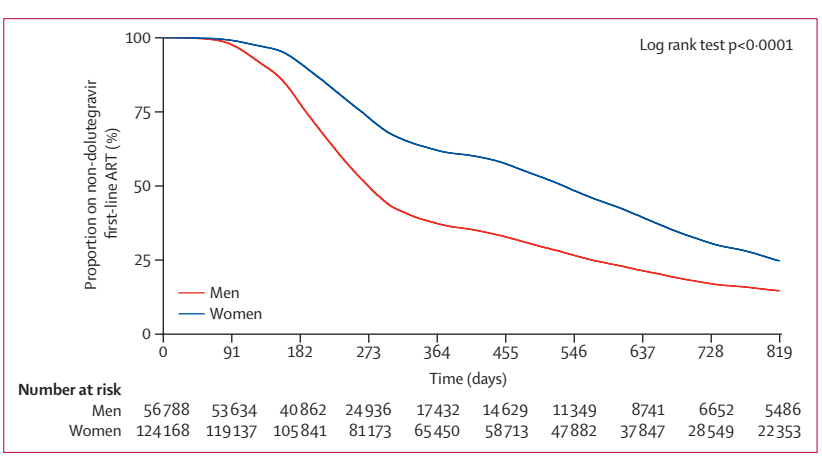

Figure 2: **Kaplan-Meier curve of transition to dolutegravir among people already receiving non-dolutegravir based first-line ART in December, 2019**
ART=antiretroviral therapy.

discontinuations due to adverse events.[16–18] However, better retention was partly driven by more clinic transfers among people receiving efavirenz, the reasons for which are not clear, but could represent people seeking more tolerable ART and better treatment at another clinic. We also found improved 12-month viral suppression with dolutegravir, particularly in people initiating ART, with the risk difference within the range seen in two clinical trials in Africa.[16,18] Among those transitioning from other first-line ART regimens (a group in which no clinical trials have been done), we only found improved viral suppression with dolutegravir among those with most recent viral loads of 200 copies per mL or greater. This finding could be because of HIV drug resistance against efavirenz among people with low level viraemia, better efficacy of dolutegravir at lower levels of adherence, or improved adherence due to better tolerability of dolutegravir.

There are few data from non-trial settings directly comparing outcomes between dolutegravir and other regimens, particularly in Africa. Public health data from Brazil showed good safety outcomes[23] and better 12-month viral suppression among people initiated on dolutegravir compared with people on efavirenz,[24] but the proportion on dolutegravir was low, and there was no assessment of retention in care. Studies from Malawi, Lesotho, and Uganda suggest low levels of dolutegravir HIV drug resistance mutations and high levels of viral suppression among people who transitioned to dolutegravir, but did not compare results with people remaining on non-dolutegravir regimens.[25–27] A retrospective cohort study of 3108 people from four African countries found that people who transitioned to dolutegravir had better viral suppression compared with those who remained on the same first-line or second-line regimen.[10] However, analyses such as this are susceptible to bias because it is difficult to choose an appropriate baseline time in the control group, whose treatment remains unchanged, resulting in baseline timepoints and viral load schedules differing between the two groups and the potential for immortal time bias. We emulated a target trial to overcome this limitation and present, to our knowledge, the largest analysis comparing outcomes after transition to dolutegravir among people on first-line ART, who are the largest group of people who will use dolutegravir globally.

South African guidelines recommend efavirenz rather than dolutegravir for people initiating ART who are receiving the standard rifampicin-containing tuberculosis treatment. However, we found that over half of those receiving tuberculosis treatment in our study did receive dolutegravir and, among this group, the beneficial effect of dolutegravir on viral suppression was even stronger compared with those without tuberculosis. The INSPIRING trial showed good tolerability and acceptable viral suppression among people receiving tuberculosis treatment who were given double doses of dolutegravir.[11] Although the extent of dolutegravir double dosing is not recorded in our data, our findings provide reassurance that co-treating tuberculosis and HIV co-infection did not compromise HIV outcomes in a high tuberculosis burden programmatic setting. Our findings are supported by a smaller cohort study that included 465 people receiving dolutegravir co-treatment alongside tuberculosis treatment, which found better viral suppression compared with people receiving co-treatment with efavirenz.[28]

To our knowledge, our study is the largest to evaluate dolutegravir uptake and compare subsequent treatment outcomes against non-dolutegravir-based regimens in a public health programme. We used data from routine public sector clinics, which provide care according to South African Department of Health guidelines, and used programmatic outcome definitions,[12] making our findings generalisable to other public sector settings (although our clinics were limited to one urban district). We directly compared both retention in care and viral suppression between dolutegravir and non-dolutegravir regimens, with precise estimates because of the large sample size. Our use of an emulated target trial in the transition cohort, with propensity score matching to balance the dolutegravir and non-dolutegravir groups, should increase comparability, although we cannot rule out residual unmeasured confounding. We are likely to have overestimated loss to follow-up as mortality and silent transfers to other clinics are underestimated in TIER.net.[29] As we used routinely collected data, we were unable to search for silent transfers to other clinics and did not have consent to search for deaths on the national registry. We assessed 12-month treatment outcomes, and further work will be required to assess whether outcomes remain similar after longer follow-up. We were unable to assess the dose of dolutegravir used in people with tuberculosis, HIV drug resistance, and adverse events such as weight gain, as these are not recorded in TIER.net.

Our findings are important as they show the extent to which women were excluded from early dolutegravir roll-out. Our findings also provide reassurance that, in programmatic settings, dolutegravir is associated with similar or better outcomes than efavirenz, reflecting findings from clinical trials. Although improvements in retention in care and viral suppression with dolutegravir were modest, incremental gains are important in reaching the 95-95-95 targets. However, overall loss to follow-up of 20% by 12 months among people newly initiating ART shows that early retention in care remains a key challenge for HIV programmes, and could limit the potential benefit of improved ART regimens. Strategies to identify and support people at risk of loss to follow-up are therefore needed. Our findings support ongoing efforts to continue the transition to dolutegravir, and to remove restrictions on dolutegravir use among people being treated for tuberculosis. Efforts should particularly focus on ensuring that women receive updated safety information and are provided the opportunity to use dolutegravir without restrictions. More broadly, strategies

to introduce newer antiretrovirals at scale should ensure that the necessary safety evidence is being generated as quickly as possible before roll-out, and that pregnant women are included in drug trials where possible. Further research is needed in non-trial settings to assess reasons for not transitioning to dolutegravir,[30] adverse events such as weight gain and metabolic consequences (which seem to disproportionately affect women),[31] the effect of transition to dolutegravir among people with viraemia of 1000 copies per mL of greater,[32] and the use of dolutegravir in second-line regimens.[33]

In conclusion, we found that young women were less likely to receive dolutegravir than men until September, 2021, and that people receiving dolutegravir had better retention in care and viral suppression compared with people receiving efavirenz. Efforts to transition to dolutegravir should continue.

Contributors

JD, YS, LL, CB, RJL, KN, CCB, and NG conceptualised the study. TK, YS, MM, and RvH oversaw data collection. TK, RG, SP, and JvdM oversaw data curation. JD, YS, TK, JvdM, RG, SP, LL, MM, RvH, and NG had full access to the data in the study through their role in eThekwini Municipality, the Health Informatics Directorate, or permissions granted to the Centre for the AIDS Programme of Research in South Africa. TK, SP, JvdM, and JD have directly accessed and verified the underlying data. JD, JvdM, LL, and CB analysed the data. JD drafted the manuscript. All authors contributed to interpretation of results and critically reviewed and edited the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

RJL has received research support from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under award numbers R01AI152772 and R01AI167699. These awards are for projects relating to the monitoring of HIV drug resistance (focused on dolutegravir resistance) and evaluation of management strategies for people with virological failure on dolutegravir-containing regimens. RJL also received support for travel to attend as a presenter at a 1-day workshop on the future of antiretrovirals in Africa (September, 2022). All other authors declare no competing interests.

Data sharing

The data used for this analysis cannot be shared publicly because of legal and ethical requirements regarding the use of routinely collected clinical data in South Africa. Researchers can request access to the data from the eThekwini Municipality Health Unit and the South African National Department of Health TB/HIV Information System (contact details obtainable upon request to JD).

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