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Initiation of Dolutegravir Versus Efavirenz on Viral Suppression and Retention at 6 months: A Regression Discontinuity Design

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Background: In 2019, South Africa's Antiretroviral Therapy (ART) Treatment Guidelines replaced efavirenz with dolutegravir in first-line ART.

Setting: We assessed the impact of this national guideline change on retention and viral suppression in the Themba Lethu Clinical Cohort, Johannesburg, South Africa. We applied a regression discontinuity design in a prospective cohort study of 1654 adults living with HIV initiating first-line ART within 12 months (±12 months) of the guideline change.

Methods: We compared outcomes in individuals presenting just before and after the guideline change and estimated intention-to-treat effects on initiating a dolutegravir- vs efavirenz-based regimen. Primary outcomes were retention and viral suppression. Participants were defined as retained in care if a visit took place within ±3 months of the 6-month end point. Viral suppression was defined as having a viral load ≤1000 copies/mL 3 months before and up to 6 months after the 6-month end point.

Results: The 2019 guideline change led to an increase in uptake of dolutegravir. We noted a 26.6 percentage point increase in the proportion initiating dolutegravir [95% Confidence Interval (CI): 14.1 to 38.6]. We saw a small increase in viral suppression [Risk Difference (RD): 7.4 percentage points; 95% CI: −1.6 to 16.5] and no change in retention (RD: −1.7 percentage points; 95% CI: −13.9 to 10.5) at 6 months, though our findings were imprecise.

Conclusions: Our estimates suggest early uptake of the revised treatment guidelines after implementation. Despite this, there was no meaningful change in viral suppression and retention rates at 6 months.

Key Words: HIV/AIDS, ART, retention, suppression, South Africa

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INTRODUCTION

With almost 8 million people living with HIV (PLWH), South Africa has the largest burden of HIV in the world.[1,2] To bring the epidemic under control, the National Department of Health seeks to achieve the UNAIDS 95-95-95 targets by 2030—meaning 95% of PLWH know their HIV status, 95% of people who know their status are receiving antiretroviral therapy (ART), and 95% of people on ART are virally suppressed (in 2022 South Africa reached 94%, 79%, and 91%, respectively).[3,4] To achieve the 95% suppression target, treatment guidelines have been updated to increase viral suppression and retention through improved medications with fewer side effects.[3,5]

In October 2019, South Africa's National ART Guidelines recommended the use of dolutegravir, an integrase-strand transfer inhibitor (INSTI), replacing efavirenz, a non-nucleoside reverse transcriptase inhibitor (NNRTI), as one of three medications in first-line ART.[5] This recommendation was based on World Health Organization guidance and results from clinical trials demonstrating dolutegravir's safety and efficacy with minimal side effects.[5–10] However, with intensive follow-up protocols and the exclusion of sicker participants, trials rarely replicate real-world settings, necessitating observational effectiveness studies. Although several observational studies evaluating the effectiveness of dolutegravir-based ART regimens have been conducted, observational research is often limited in its ability to identify causal effects because of confounding and selection bias.[11–16] Furthermore, some have been in high-income countries and/or have not used efavirenz as a comparator.[11–13] Evaluating dolutegravir's impact on retention and suppression will be key in understanding our progress toward the last 95 target.

To address this gap in the literature, we sought to assess the effect of initiating a dolutegravir-based regimen, compared with an efavirenz-based regimen on 6-month viral suppression and retention in care among adults initiating first-line ART in Johannesburg, South Africa, from 2019 to 2020 using a regression discontinuity design.[17–19]

METHODS

Data Source

We used data from the Themba Lethu HIV Clinical Cohort, a public-sector comprehensive HIV care and treatment clinic. The cohort has been described previously.[20] In brief, the clinic is located at the Helen Joseph Hospital, a large urban secondary-level public teaching hospital in Johannesburg.[20] The cohort was established in 2004 and has initiated close to 40,000 participants onto ART to date according to South Africa's National ART guidelines for adolescents and adults.[5,20] Before the guideline change in 2019, the clinic's first-line ART medications were tenofovir disoproxil fumarate/lamivudine/efavirenz and tenofovir disoproxil fumarate/emtricitabine/efavirenz.[5] After the guideline change, efavirenz was replaced by dolutegravir in these three-drug ART combinations.[5]

As of 2010, participants receiving ART at Themba Lethu received viral load testing 6 months after initiating ART and then yearly thereafter.[20] Participants typically pickup ART medications monthly for first 6 to 12 months of treatment and then every 2 months once stable. All demographic, laboratory, and clinical information is entered into TherapyEdge-HIV, a real-time data capturing system used by the clinic, during the participant's visit.[20]

Study Population

We conducted a prospective cohort study using a regression discontinuity design.[17,19,21–23] The study population included participants who were treatment naive, aged $\geq$16 years, and newly initiating an efavirenz- or dolutegravir-based ART regimen within $\pm$ 12 months of January 2020, (ie, January 2019—December 2020), the date of implementation of the new guidelines at the clinic. People who were pregnant at the time of treatment initiation were excluded because they are often referred for treatment to an antenatal clinic focused on providing HIV care and treatment to individuals during the course of their pregnancy.

Exposure

We created an assignment variable to identify whether participants initiated their ART regimen before or after the policy change (January 1, 2020). The assignment variable was equal to 1 if ART initiation was on or after dolutegravir rollout in first-line ART and 0 if ART initiation was before dolutegravir rollout in first-line ART. In addition, we created a variable to indicate the treatment participants actually received: an efavirenz- or dolutegravir-based regimen. The other 2 drugs in the regimens were either lamivudine/tenofovir disoproxil fumarate (nucleoside reverse transcriptase inhibitor/non-nucleoside reverse transcriptase inhibitor) or emtricitabine/tenofovir disoproxil fumarate (nucleoside reverse transcriptase inhibitor/non-nucleoside reverse transcriptase inhibitor).

Outcomes

Our primary outcomes were (1) viral suppression and (2) retention at 6 months. Viral suppression at 6 months was defined as having a viral load $\leq$ 1000 copies/mL 3 months before and up to 6 months after the 6 month end point. This definition was used to allow for variation in the timing of when viral loads are collected. A participant was considered retained in care if a visit took place within $\pm$ 3 months of the 6-month end point, allowing for variation in when participants schedule their clinic appointments. We also assessed the overall frequency of treatment interruptions and single drug substitutions in our analytic cohort. Treatment interruption was defined as when treatment is stopped for any duration of period. Single drug substitution was defined as replacing 1 drug in the 3-drug regimen with another within the same drug class during the first 12 months of treatment initiation.

Statistical Analysis

South Africa's 2019 policy change in ART guidelines substituting efavirenz with dolutegravir in first-line ART

created a natural experiment allowing us to assess the effect of initiating a dolutegravir-based regimen compared with an efavirenz-based regimen using a regression discontinuity design.[17–19,21–25] Characteristics of participants initiating treatment before and after the policy change should be continuous over the cutoff that would indicate that measured and unmeasured confounders are balanced and, therefore, the assumption of continuity of outcomes is not violated.[17,25] The decision for a participant to initiate treatment on any given day in relation to the date of the policy change is a product of a variety of factors related to seeking care, such as transportation availability, for example. Therefore, as long as neither the participant nor the clinician manipulated the dates of ART initiation (e.g., delayed treatment so a participant could start a different ART regimen), participants on either side of the policy change should be exchangeable on both observed and unobserved characteristics.[17]

To evaluate whether this assumption was met in our cohort, we evaluated the distribution of baseline covariates just before and after the threshold for continuous and dichotomous covariates.[26] A histogram of the dates of ART initiation was created to visually evaluate bunching (ie, data manipulation) of the assignment variable on either side of the threshold. Evidence of bunching would be observed if the dates of ART initiation were systematically manipulated by the clinician or patient and an extremely large number of patients initiating treatment was observed immediately after the date of the policy change and an extremely small number of patients initiating treatment was observed immediately before the date of the policy change. We further used a McCrary Density test that formally assesses evidence of bunching to the right of the threshold.[26,27] For the purposes of evaluating modeling assumptions, an alpha value of 0.05 was used to identify the presence of bunching. If these assumptions are not violated and a discontinuity is seen at the threshold (ie, at the date of the policy change there is a break before and after the date), we are able to estimate the intent-to-treat (ITT) effect of initiating a dolutegravir-based regimen on viral suppression and retention at 6 months using local linear regression models with robust 95% confidence intervals (Equation 1).

$$E\,[Y|Z] = b_0 + b_1{*}(Z - c) + b_2{*}T + b_3{*}((Z - c){*}T). \quad (1)$$

We used the same simple linear regression equation to model the treatment participants actually received, our outcomes of viral suppression and retention at 6 months, and our observed covariates. In these models, Y is the outcome (ie, probability of treatment received, suppression, or retention), b_0 is the intercept, Z represents the date of each participant's treatment initiation, c is the date of the policy change, T is the assignment variable, equal to 0 or 1, that indicates whether a participant initiated treatment before ($T = 0$) or after the policy change ($T = 1$), and b_2 is the ITT effect of treatment. The date of each participant's treatment initiation is centered by subtracting the date of the guideline change (ie, Z—c). An interaction term (ie, (Z—c) * T) between the date of treatment initiation and the assignment variable is used to allow for different slopes before and after the policy change. The models were generated using Stata's *rdrobust* package.[28] The optimal biased bandwidth for the analysis was determined by Stata's *rdbwselect* function, a data-driven approach, to determine the optimal area around the threshold where patients are most likely to be exchangeable.[29] Ensuring patients are exchangeable right before and after the policy change (eg, local randomization) is a key assumption that must be met for the regression discontinuity design. For visual representation, linear regression plots for the probability of treatment received and for each outcome (ie, suppression and retention) were overlaid with scatterplots binned in 60-day intervals, with the probability of treatment received and the average outcome in each bin displayed. Complier average causal effect (CACE) estimates were then determined by estimating the effect of initiating a dolutegravir-based regimen among participants whose regimen was based on the policy change.[25] The CACE is calculated by dividing the ITT by the probability of initiating a dolutegravir-based ART regimen.

Sensitivity Analyses

To check the robustness of our estimates, we conducted the following checks: (1) assumed that those with a missing viral load at 6 months were virally unsuppressed, (2) removed participants who initiated within ± 14 days of the policy change, (3) used the unbiased bandwidth, and (4) removed each bin.

Ethics Statement

Data on participants from Themba Lethu Clinic were collected for routine clinical purposes and the study team had no direct contact with participants. Use of data was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M140201). Approval for analysis of deidentified data was also granted by the Institutional Review Board of Boston University (H-29768). An informed consent waiver for analysis of deidentified data was received from the Boston University's Institutional Review Board and the Human Research Ethics Committee of the University of the Witwatersrand.

RESULTS

Validity of the Regression Discontinuity Design

A total of 1654 participants initiating either a dolutegravir-based or an efavirenz-based regimen within 12 months of the guideline change were included. Predicted values of observed clinical and demographic characteristics were similar for participants initiating ART just before and after the policy change (Table 1), consistent with the assumption of local randomization. Except for baseline body mass index (BMI) and hemoglobin, levels of missingness were similar across characteristics. However, the observed BMI and hemoglobin were similar for both groups (Table 1).

TABLE 1. Predicted Values of Observed Characteristics Just Before and After the Threshold (January 2020) (N = 1654)

	Just before January 2020 (n = 937)	Just after January 2020 (n = 717)
Age (Yrs)	39.0	39.7
Missing, n (%)	0	0
Female sex (%)	45.6	47.7
Missing, n (%)	0	0
CD4 cell count (cells/mm^3)	247.0	278.1
Missing, n (%)	153 (16.3)	147 (20.5)
Baseline BMI (kg/m^2)	24.7	24.7
Missing, n (%)	286 (30.5)	337 (47.0)
Baseline weight (kg)	65.0	65.7
Missing, n (%)	282 (30.1)	268 (37.4)
Baseline systolic (mm Hg)	124.2	124.1
Missing, n (%)	248 (26.5)	259 (36.1)
Baseline diastolic (mm Hg)	81.3	80.7
Missing, n (%)	248 (26.5)	259 (36.1)
Baseline hypertension* (%)	16.8	18.4
Missing, n (%)	0	0
Baseline hemoglobin (g/dL)	11.6	12.0
Missing, n (%)	329 (35.1)	617 (86.1)

*Hypertension diagnosis based off a systolic blood pressure >90 mm Hg and/or a diastolic blood pressure >140 mm Hg or being prescribed antihypertensive medication.

Furthermore, evaluation of baseline clinical and demographic characteristics for those missing and not missing a baseline hemoglobin/BMI was similar indicating that our assumption of local randomization is met (Tables 2–3, Supplemental Digital Content, http://links.lww.com/QAI/C452). A histogram of ART initiation dates was created to visually assess potential bunching (eg, data manipulation), around the threshold. This was done by evaluating whether there was a sharp increase or decrease in the number of patients initiating treatment immediately after the policy change compared with just before. Evidence of bunching would suggest systematic manipulation by clinicians or patients. Although evaluation of the histogram indicated a small increase in the decrease in the number of patients initiating ART after the policy change compared with just before, the McCrary Density Test did not find evidence of data manipulation (P-value = 0.07; Fig. 1). This small increase is likely because participants are much less likely to go to the clinic during the holiday period (December—January), so the uptick right after the policy change is likely because of the holiday period and not manipulation of dates of initiation (Fig. 1B).

The 2019 guideline change led to a 26.6 [95% confidence interval (CI): 14.1 to 38.6] percentage point increase in the proportion of participants initiating a dolutegravir-based ART regimen at the threshold (Fig. 2A). There were no other major policy changes in South Africa during this time because universal test and treat were implemented in 2016, and same day initiation was implemented in 2017; no other major changes have been made since then.[30–32] Therefore, we believe the assumptions of the regression discontinuity design were met.

Overall

Among the 937 participants who initiated treatment before the guideline change, 75 (8.0%) initiated a dolutegravir-based regimen and 862 (92.0%) initiated an efavirenz-based regimen. Among the 717 participants who initiated treatment after the guideline change, 570 (79.5%) initiated a dolutegravir-based regimen and 147 (20.5%) initiated an efavirenz-based regimen. Among participants who initiated a dolutegravir-based regimen, 60.5% were retained and 94.5% achieved viral suppression at 6 months. Among participants who initiated an efavirenz-based regimen, 59.9% were retained and 89.6% achieved viral suppression at 6 months.

Furthermore, 7% of patients in our analytic cohort experienced a treatment interruption. Treatment interruption occurred a median of 84 days [Interquartile Range (IQR): 28–209] after treatment initiation and lasted for a median of 83 days (IQR: 27–168). Reasons for treatment interruption were not reported. Among patients on tenofovir, 4.0% were substituted with either abacavir or tenofovir. In addition, 3.0% of patients replaced lamivudine with emtricitabine, while 14.0% of patients initially on emtricitabine replaced it with lamivudine.

Intent-To-Treat Estimates

Results from the regression discontinuity analysis found no change in retention (Risk Difference: −1.7, 95% CI: −13.9 to 10.5) and a small increase in viral suppression at 7.4 percentage points (95% CI: −1.6 to 16.5) 6 months after initiating onto a dolutegravir-based ART regimen, though our findings were imprecise (Figs 2B, C) and largely consistent with little overall change in either outcome. It is important to note that receiving a viral load test is a function of retention because participants who are not retained at 6 months will not have a viral load conducted. The percentage of missing viral load before and after the guideline change was similar with 44% missingness before and 47% missingness after the policy change. CACE estimates are detailed in Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C452. However, owing to the null effect observed in the ITT estimates, we chose not to focus on the CACE.

Sensitivity Analyses

We conducted 4 separate sensitivity analyses. First, we assumed those with a missing viral load to be virally unsuppressed. Second, we removed participants who initiated ± 14 days of the policy change. Results from these analyses, while more conservative, were broadly similar and did not substantively change the conclusions of our findings (Figures 1–3, Supplemental Digital Content, http://links.lww.

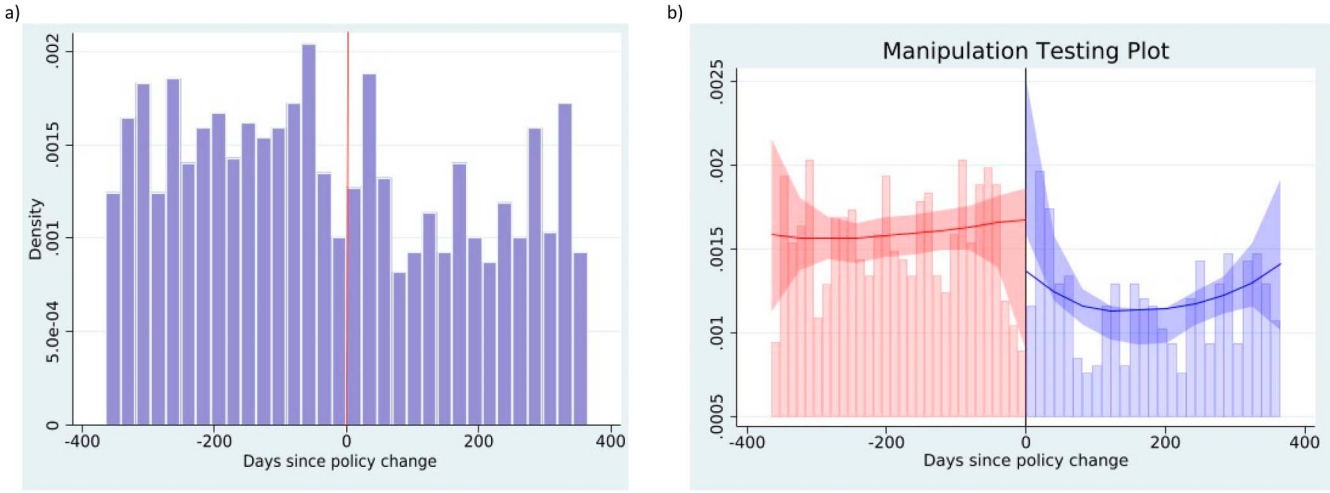

FIGURE 1. A, Histogram of number of participants initiating treatment relative to the date of the guideline change. B, McCrary Density Plot to evaluate the presence of bunching using a bandwidth that is 1 standard deviation away from the mean (*P*-value = 0.07).

com/QAI/C452). Third we conducted the analysis using the unbiased bandwidth, and finally we removed each bin. Results from the unbiased bandwidth and removing each bin were more imprecise because they used a smaller subset of the 1,654 participants, but did not change the conclusions of our findings.

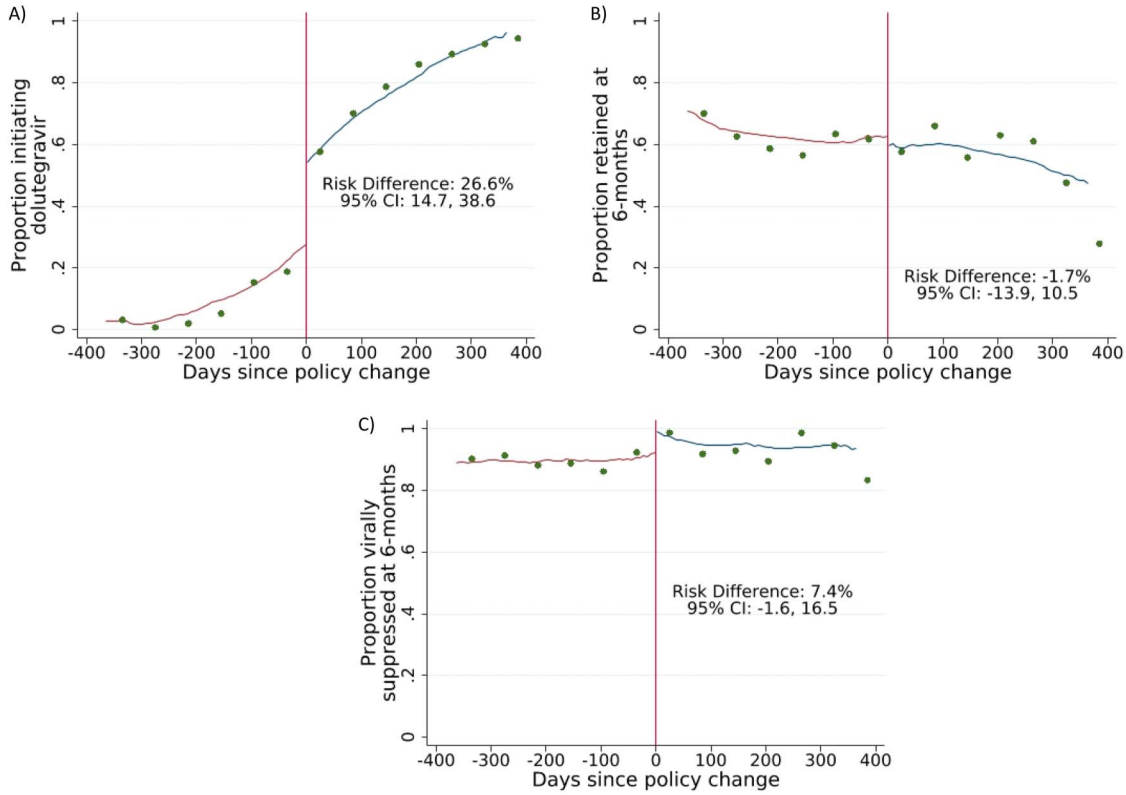

FIGURE 2. A, Probability of receiving dolutegravir as first-line ART among treatment-naive participants receiving care at Themba Lethu Clinic, South Africa (N = 1654, RD: 24.6%, 95% CI: 6.1 to 43.1). The biased MSERD (b) bandwidth of 180 was used. B, Proportion of participants who are retained at 6 months (RD: −6.9% 95% CI: −23.7 to 9.9; b 219). C Proportion of participants who are virally suppressed at 6 months (RD: 7.7% 95% CI: −6.3 to 21.6; b: 168). The red line represents the date of the guideline change.

DISCUSSION

Our estimates suggest early uptake of South Africa's revised treatment guidelines at the Themba Lethu Clinic because there was a large and sharp increase in the proportion of participants initiating onto a dolutegravir-based regimen after implementation of the guideline change. Overall, our findings suggest that there is no meaningful change in retention or viral suppression at 6 months for those initiating a dolutegravir-based regimen compared with those initiating an efavirenz-based regimen. However, our findings lacked precision, largely because of the small sample size. Clinical trials have found that over the long term (96 weeks), rates of viral suppression were similar with no meaningful difference between participants initiating a dolutegravir-based regimen and participants initiating an efavirenz-based regimen.[6,10,33,34] Therefore, although our findings at 6 months are less precise, they are consistent with findings from clinical trials. A meaningful change in retention and viral suppression between patients initiating a dolutegravir-based regimen and patients initiating an efavirenz-based regimen is likely a 5-percentage point change, given the UNAIDS transition from the 90-90-90 targets to the 95-95-95 targets indicates a 5-percentage point increase is important.[3] However, we do want to note that any increase in retention and viral suppression is beneficial in the current context because these benefits extend beyond the individual patient's health outcomes and extend to prevention of new infections that is a priority for ending the HIV epidemic.

The major strength of our study is the use of a quasi-experimental approach. A regression discontinuity design allows us to generate causal effect estimates without strong and/or untestable assumptions that are often present in other epidemiologic approaches that use observational cohort data. Our approach compares the outcomes of 2 populations: participants initiating treatment right before and after the guideline change. These 2 populations should be similar on observed and unobserved factors near the threshold because of the design of the regression discontinuity. Prior research evaluating the effect of dolutegravir using observational data has not used such an approach and, therefore, is at risk of confounding and selection bias.[11–16] In addition, there were no other major changes in guidelines during this time period, allowing us to be certain that the changes seen here are solely because of the treatment guidelines recommending the use of a dolutegravir-based regimen over an efavirenz-based regimen.

However, our study has several limitations. Most notably our small sample size (N = 1654) led to imprecise and unstable estimates as noted by the wide confidence intervals and the change from a 1.7 percentage decrease in retention in our primary analysis to a 0.5 percentage increase in retention in our sensitivity analysis after removing participants who initiated within 14 days before and after the policy change. Furthermore, owing to the COVID-19 pandemic, patients who initiated in 2020 (eg, after implementation of the policy change) may have been unable to attend a 6-month clinic visit and/or have a viral load conducted because frequency of visits to the clinic was reduced as a precaution. Although we provided windows of 3 months or greater on either side of the 6-month date for both outcomes, there could still be a number of patients who initiated dolutegravir who would be considered not retained and/or not virally suppressed because of this reduced clinic visit scheduling. In combination with the imprecision of these estimates, it makes it difficult to truly determine whether there are any meaningful differences in retention and suppression outcomes for participants initiating treatment. Therefore, our results should be interpreted with caution because our findings could be due to random variation from our small sample size. Second, we were unable to evaluate longer term outcomes at 18 and 24 months that is when some effects of ART may become more apparent. This is partly because of the overlap between the implementation of the new treatment guidelines and the COVID-19 pandemic. Policies enacted during the COVID-19 pandemic meant that many patients experienced reduced frequency of clinic visits, therefore, many of the participants who initiated onto a dolutegravir-based regimen did not have data observed at the 18- and 24-month milestones. Third, because having a viral load conducted means a patient needs to be retained in care, viral load is conditional on being retained. Therefore, patients who do have a viral load are often more likely to be virally suppressed because being retained in care inherently increases the likelihood a patient is adherent to medication as they are attending clinic visits. Patients who are not retained are less likely to be virally suppressed because they are not attending clinic visits and are unable to pick-up their ART medications. Our estimates suggest the guideline change led to a small, possibly negligible, decrease in retention and so the population who remained in care may differ slightly in terms of viral suppression compared with those who did not remain in care. However, our sensitivity analysis where we assumed that patients who were missing a viral load were virally unsuppressed did not substantively change the conclusions of our findings. Fourth, there was a high proportion of missing observable baseline characteristic data that may have affected our interpretation of balance before and after the policy change. However, the proportions of missingness did not differ before and after the policy change. Therefore, it is likely that missingness is random at the threshold and unlikely to have meaningfully biased our estimates.[26,27] Fifth, the assignment variable in this study was time, as such there is an increased risk of clinicians and/or participants manipulating the assignment variable because of advanced knowledge of the policy change in comparison with other studies that use strict cutoffs.[17] Finally, given that this study was conducted in a single urban center in Johannesburg, these findings may not be applicable to other settings in South Africa such as rural areas because retention rates may differ depending on location.

Our findings suggest that there is no meaningful difference in retention and viral suppression outcomes for participants initiating onto a dolutegravir-based regimen compared with those initiating an efavirenz-based regimen. Evaluation of larger cohorts and longer term outcomes is key to understanding the impact of policy shift on continuity of care and sustained viral suppression,[35,36] both of which are

key to helping South Africa achieve its 95-95-95 targets by 2030.[3,37] Finally, there is an association between modern, better tolerated regimens such as dolutegravir and increased weight gain, which subsequently increases a participant's risk for hypertension and diabetes.[38–40] Future work to evaluate the risk of these outcomes and the impact of such comorbidities on long-term ART adherence and retention is needed.

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