American Journal of Epidemiology
© The Author(s) 2018. Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.
Vol. 187, No. 9
DOI: 10.1093/aje/kwy093
Advance Access publication:
May 15, 2018

Practice of Epidemiology

Medication Side Effects and Retention in HIV Treatment: A Regression Discontinuity Study of Tenofovir Implementation in South Africa and Zambia

Alana T. Brennan*, Jacob Bor, Mary-Ann Davies, Gilles Wandeler, Hans Prozesky, Geoffrey Fatti, Robin Wood, Kathryn Stinson, Frank Tanser, Till Bärnighausen, Andrew Boulle, Izukanji Sikazwe, Arianna Zanolini, and Matthew P. Fox

* Correspondence to Dr. Alana T. Brennan, Department of Global Health, School of Public Health, Boston University, Crosstown Center, 3rd Floor, Room 392, 801 Massachusetts Avenue, Boston, MA 02118 (e-mail: abrennan@bu.edu).

Initially submitted July 31, 2017; accepted for publication April 18, 2018.

Tenofovir is less toxic than other nucleoside reverse-transcriptase inhibitors used in antiretroviral therapy (ART) and may improve retention of human immunodeficiency virus (HIV)–infected patients on ART. We assessed the impact of national guideline changes in South Africa (2010) and Zambia (2007) recommending tenofovir for first-line ART. We applied regression discontinuity in a prospective cohort study of 52,294 HIV-infected adults initiating first-line ART within 12 months (±12 months) of each guideline change. We compared outcomes in patients presenting just before and after the guideline changes using local linear regression and estimated intention-to-treat effects on initiation of tenofovir, retention in care, and other treatment outcomes at 24 months. We assessed complier causal effects among patients starting tenofovir. The new guidelines increased the percentages of patients initiating tenofovir in South Africa (risk difference (RD) = 81 percentage points, 95% confidence interval (CI): 73, 89) and Zambia (RD = 42 percentage points, 95% CI: 38, 45). With the guideline change, the percentage of single-drug substitutions decreased substantially in South Africa (RD = −15 percentage points, 95% CI: −18, −12). Starting tenofovir also reduced attrition in Zambia (intent-to-treat RD = −1.8% (95% CI: −3.5, −0.1); complier relative risk = 0.74) but not in South Africa (RD = −0.9% (95% CI: −5.9, 4.1); complier relative risk = 0.94). These results highlight the importance of reducing side effects for increasing retention in care, as well as the differences in population impact of policies with heterogeneous treatment effects implemented in different contexts.

Africa; antiretroviral therapy; human immunodeficiency virus; low- and middle-income countries; regression discontinuity; stavudine; tenofovir; treatment outcomes

Abbreviations: ART, antiretroviral therapy; CACE, complier average causal effect; HIV, human immunodeficiency virus; IeDEA, International Epidemiological Databases to Evaluate AIDS in Southern Africa; ITT, intention-to-treat; WHO, World Health Organization.

Billions of dollars are invested in pharmaceutical research and development annually to identify medications with efficacy comparable to that of existing drugs but with fewer side effects (1–3). Currently, there are over 30 antiretroviral drugs in development to help treat and prevent human immunodeficiency virus (HIV) infection (4). Most of these drugs seek to improve clinical outcomes not through increased efficacy but through improved adherence and retention as a result of reduced toxicity (4). Adverse reactions to treatment are a major cause of nonadherence to antiretroviral therapy (ART) and poor retention in care (5–7). Although there may be clear benefits to patient quality of life, evidence on the clinical impact of these newer drugs is normally limited to demonstration of noninferiority in a controlled trial setting (8–16). The clinical benefits of less toxic regimens (e.g., improved adherence and retention) are rarely measured in real-world nontrial settings (17–28). Furthermore, because patients may respond differently to medications, clinical benefits may vary across populations.

In 2004, the World Health Organization (WHO) recommended the use of stavudine in first-line ART in low- and middle-income countries (29). By 2007, clinical trials had shown that tenofovir-based regimens, which had been used in

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

high-income countries for years, were comparable in terms of efficacy and had a better toxicity profile than stavudine-based (15, 30) or zidovudine-based (15) regimens. Adverse reactions, including dyslipidemia, lipoatrophy, peripheral neuropathy, and hyperlactatemia, were observed in 5%–20% of patients initiating stavudine (30–35). As such, in 2010, the WHO recommended the use of tenofovir in first-line ART in low- and middle-income countries, citing the potential harms that could result if side effects led HIV patients to default therapy, including adverse patient outcomes and the potential for development of drug-resistant strains of the virus (36). By 2012, 80% of low- and middle-income countries had implemented the guidelines, replacing stavudine with tenofovir or zidovudine in first-line ART (5, 36).

It was expected that initiating the use of tenofovir in HIV patients would lead to improved adherence and reduced loss to follow-up (36), with implications for longer-term health outcomes (37). However, the impact of initiating tenofovir as the standard of care on patient outcomes has only been evaluated in observational studies. Those studies have consistently found a protective association between tenofovir use and single-drug substitution (13–20, 38), a widely used marker for adverse reactions to treatment. Yet many of these same observational studies reported mixed results for the association between initiating tenofovir and death, loss, and immunological or virological response (17–19, 22). Existing studies were performed at single sites and typically well-resourced clinics, limiting generalizability of the findings (17–20, 38). Studies conducted prior to the change in the guidelines (17, 18) focused mainly on effects of tenofovir in the subpopulation of patients receiving tenofovir due to contraindications to the use of stavudine and/or zidovudine and may not be informative regarding treatment effects for the larger population of patients initiating tenofovir as the standard of care after the guideline changes. Finally, and most importantly, prior studies used methods which may be vulnerable to confounding by indication; for example, pancreatitis, kidney disease, and obesity are contraindications to stavudine but are also associated with poor HIV treatment outcomes (39). As a result, comparisons between patients initiating tenofovir and those not initiating it in the existing literature may be biased.

We used a regression discontinuity study design (40–43) to evaluate the impact of the policy change, comparing patients starting ART immediately before and after the guideline changes in South Africa and Zambia. We assessed the impact of the guideline change on whether patients started tenofovir, as well as on key clinical outcomes: attrition, death, virological failure, and CD4-positive T-cell response. The guideline change offered a rare natural experiment with which to evaluate the clinical impact of scaling up a drug valued not just for its efficacy but also for its lower toxicity profile in comparison with prior drugs.

METHODS

Data source

Data were obtained from International Epidemiological Databases to Evaluate AIDS in Southern Africa (IeDEA)–Southern Africa (www.iedea-sa.org), a collaboration of HIV treatment cohorts in southern Africa (44). We included cohorts from the Gugulethu, Hlabisa, Khayelitsha, and Themba Lethu ART programs and Tygerberg Hospital in South Africa and the Centre for Infectious Disease Research cohort in Zambia. Some IeDEA clinics from South Africa and Zambia stopped reporting to IeDEA shortly after the guideline changes were issued and were excluded from the analysis.

Investigators at all IeDEA-Southern Africa sites obtained ethical approval from relevant local institutions. Boston University's Medical Campus Institutional Review Board granted approval of secondary analyses of deidentified data.

Study design

We conducted a prospective cohort study using a regression discontinuity design. The study sample included ART-naive HIV-infected patients aged ≥16 years initiating first-line ART. In South Africa, immediate ART eligibility was extended to pregnant women and to patients with tuberculosis and hepatitis B virus coinfection at the same time as tenofovir was incorporated into first-line therapy. To mitigate against the potential for bias resulting from this concurrent policy change, we excluded pregnant women and patients diagnosed with tuberculosis at treatment initiation from our analysis, where possible. Screening for hepatitis B was rare at the time and was not included in the database. As a test for the similarity of the study population before and after the tenofovir policy change, we assessed trends in baseline CD4 cell count at initiation (after the above exclusions). If the eligibility expansion changed the composition of the sample, we would see an increase in the average CD4 count. As described below, we found no gap in CD4 count at the threshold. We also conducted a detailed review of HIV treatment guideline changes and identified no other major changes during the period of study. There were no other major policy changes in Zambia. Patients were included in the analysis if they initiated ART within the period comprising 12 months before and after (±12 months) the guideline changes. Guideline changes occurred on April 1, 2010, in South Africa (45) and July 1, 2007, in Zambia (46, 47). Some facility-level variation occurred when the guidelines were rolled out in Zambia (all within ±3 months of July 1, 2007); as such, we used facility-specific implementation dates in our analysis of the Zambian data to assign patients to the guidelines that were in effect on the date they initiated ART. All patients had the potential for at least 24 months of follow-up after the date of initiation.

Exposures

Exposure to the guideline change (tenofovir as the standard of care) was defined as an indicator variable equal to 1 if the patient initiated ART on or after the guideline change date and 0 otherwise. In addition, we defined an indicator variable for whether the patient initiated tenofovir as part of first-line ART.

Outcomes

Our primary outcomes were single-drug substitutions (defined as a change of the nucleoside reverse-transcriptase inhibitor within first-line ART, without other medication changes) and attrition from care (defined as not having made a clinic visit within

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

6 months prior to the closure date of each program). Single-drug substitution was the standard of care in both countries for patients experiencing an adverse reaction to the initially prescribed nucleoside reverse-transcriptase inhibitor (45, 46). The extent of the occurrence of single-drug substitution depended on the availability of less toxic replacements. Patients who switched to second-line ART (defined as switching the nucleoside reverse-transcriptase inhibitor and replacing the nonnucleoside reverse-transcriptase inhibitor with a protease inhibitor) (36) were censored at the start of second-line ART.

As secondary outcomes, we assessed death, CD4-positive T-cell response, and viral load failure, all evaluated over the course of 24 months. Mortality in South Africa was ascertained via family or hospital report, active tracing, and/or linkage with the South African National Vital Registration System (48, 49). Zambia does not have a death registry; mortality was ascertained via family or hospital report or via active tracing. Mortality estimates were not weighted to account for rates of death among persons lost to follow-up. In both countries, mortality ascertainment may be incomplete. Patients established on ART were monitored for viral load (in South Africa) and CD4-cell response (in both countries) (45, 46). Viral load failure was defined as 2 consecutive viral loads, measured at least 2 weeks apart, greater than 400 copies/mL (45). The first elevated viral load measurement had to fall within the first 18 months on ART with a window of ±6 months, with documentation of the second viral load measurement confirming failure within 24 months (±6 months) for patients who were alive and in care. The first elevated viral load was considered the date of failure. CD4-cell response was calculated as the mean change in CD4 count from ART initiation to 24 months on treatment. The first CD4 count in the 6-month window around 24 months of follow-up for those patients alive and in care was used. To assess longer-term outcomes, we analyzed attrition, death, single-drug substitution, and immune response over the course of 48 months in Zambia; there was insufficient follow-up time to assess outcomes beyond 24 months in South Africa.

Statistical analysis

We used a regression discontinuity design (40–43, 50–54) to compare patients initiating ART just before and after the WHO guideline changes. Characteristics of patients initiating ART just before the guideline changes versus just after the guideline changes were expected to be continuous over the cutoff, demonstrating balance in both observed and unobserved covariates (similar to a clinical trial), providing confidence that the assumption of continuity of potential outcomes was not violated. The precise date of initiation—and thus, whether a patient initiated ART before or after the guideline change—was a product of random factors related to the decision to seek care, weather and transport conditions, arrival of laboratory results, and clinic congestion (among others). So long as dates of ART initiation were not manipulated by either the patient or the clinician in order to gain access to tenofovir, patients on either side of the threshold should have been exchangeable. The guideline changes thus offered a natural experiment for evaluating the impact of tenofovir implementation as the standard of care on patient outcomes. In contrast to a simple pre-/post- analysis, which can be confounded by secular trends, we focused our comparison on patients initiating ART immediately before and after the date of the guideline changes. Note that some patients initiated treatment with tenofovir even before the guideline changes, and not all patients initiated tenofovir afterwards. Thus, we analyzed the impact of the guideline change from an intention-to-treat (ITT) perspective. We also used instrumental-variables methods to uncover the effect of initiating tenofovir on those patients whose initiating regimen was determined by the guideline change, known as the complier average causal effect (CACE) (41).

ITT effects were estimated separately for each country and each outcome on a risk difference scale using local linear regression models with heteroskedasticity-robust standard errors. We controlled for continuous linear trends in outcomes over time with respect to date of initiation, allowing for separate slopes before and after the guideline change. We overlaid scatterplots binned in weekly intervals, displaying the average outcomes in each bin. Our ITT treatment effect was estimated as the intercept shift on the date of the guideline change (i.e., the coefficient on the threshold indicator). A data-driven optimal bandwidth was calculated for each outcome using the Imbens and Kalyanaraman (55) bandwidth selector. Due to imprecision in the implementation of the guidelines, we excluded patients initiating ART within 14 days before and after (±14 days) the guideline change when calculating our primary estimates. The CACE was estimated using the threshold indicator as an instrument for whether the patient actually initiated tenofovir. We estimated the CACE by dividing the ITT by the first-stage estimates, using separate optimal bandwidths for each. We also estimated the treatment complier mean and the complier relative risk of attrition for those patients whose first-line regimen was determined by the guideline change. We obtained 95% confidence intervals for the CACE and the complier relative risk using the percentile bootstrap method (1,001 bootstrap samples) (56, 57).

To assess the comparability of patients initiating ART just before and after guideline change, we assessed differences in observed baseline clinical and demographic characteristics using regression models similar to the ITT, where instead of regressing the outcome on the model parameters we regressed each baseline observable variable separately (58). As with a baseline table in a randomized trial, similarity in observed characteristics on either side of the threshold generates confidence that treatment was (quasi-) randomly assigned for patients initiating ART close to the date of the guideline change. If this assumption is supported, then there is no strong rationale (from the perspective of bias) to include covariates in the regression model, as it is assumed to be unconfounded, similar to a clinical trial. Additionally, to assess whether dates of initiation were systematically manipulated by the patient or the clinician, we conducted the McCrary density test (58) to help establish that manipulation of the start date was not an issue in our cohort. We also plotted a histogram of initiation dates and visually analyzed the distribution for evidence of bunching on one side of the threshold (58, 59).

Robustness checks

To check the robustness of our estimates, we conducted the following checks: 1) using national, rather than clinic-specific, dates of policy implementation in Zambia only; 2) including

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

patients who initiated ART within 14 days (±14 days) of the policy change; and 3) changing the bandwidths used in the linear models to one-half and twice the size of the optimal bandwidth we show in our main results in both countries. For each of these robustness checks, we estimated the 1) change in the proportion of patients initiating tenofovir, 2) change in the proportion of patients with single-drug substitutions, and 3) change in the proportion of loss to follow-up and death combined.

RESULTS

Validity of the regression discontinuity design

A total of 16,179 patients in South Africa and 36,115 patients in Zambia were included. Observed clinical and demographic characteristics were similar for patients initiating ART immediately just before and just after the guideline change in both countries (Table 1), consistent with a data-generating process in which patients on either side of the threshold were exchangeable. A threat to validity in regression discontinuity is the potential for systematic manipulation of the assignment variable—for example, in order to gain access to the intervention. Inspection of the distribution of ART starting dates (Figure 1) showed a small drop in the number of patients initiating ART during the week immediately after the guideline change, with the number increasing in weeks 2–4 to levels seen in the weeks prior to the guideline change in both countries (Figure 1). However, this pattern is not consistent with clinicians' holding back patients from initiating ART until after the guideline change, and it may rather reflect delays in the supply chain to support the guideline change.

Results also show low numbers of ART initiations in January during the holiday period in South Africa (Figure 1A). Additionally, the McCrary density test revealed no bunching before or after the threshold ($P \geq 0.05$), which is consistent with no systematic manipulation in either South Africa or Zambia (see Web Figure 1, available at https://academic.oup.com/aje). Even with these variations, we believe that there was no strong evidence suggesting systematic manipulation of initiation dates in either country. Additionally, the proportion of patients initiating tenofovir increased strongly with the guideline changes in both countries: from 7.7% to 89.0% in South Africa (risk difference (RD) = 81.0 percentage points, 95% confidence interval (CI): 73.0, 89.0) and from 7.0% to 49.0% in Zambia (RD = 42.0 percentage points, 95% CI: 38.0, 45.0) (Figure 2). This dramatic uptake of tenofovir in both countries at the threshold lends credence to the view that regression discontinuity is an appropriate design for assessing the impact of the guideline change on our desired outcomes.

ITT estimates

The change in guidelines resulted in an ITT decrease in single-drug substitutions during the first 24 months on ART, from 19.0% to 4.0%, in South Africa (RD = −15.0 percentage points, 95% CI: −18.0, −12.0) (Figure 3) and a small decrease from 7.0% to 4.7% in Zambia (RD = −2.3 percentage points, 95% CI: −3.6, −0.3) (Figure 4) at the threshold. Rates of single-drug substitution differed quite substantially across the countries prior to the policy change, perhaps due to the prepolicy

Table 1. Predicted Values of Observed Clinical and Demographic Characteristics as the Date of Antiretroviral Therapy Guideline Change is Approached From Just After and Just Before the Threshold in South Africa (2010) and Zambia (2007)

Variable	Country											
	South Africa (n = 16,179)						Zambia (n = 36,115)					
	Just After April 2010	No. of Values Missing	% of Values Missing	Just Before April 2010	No. of Values Missing	% of Values Missing	P Value	Just After July 2007	No. of Values Missing	% of Values Missing	Just Before July 2007	No. of Values Missing	% of Values Missing	P Value
Age, years	36.7	0	0	36.0	0	0	0.067	34.3	0	0	34.5	0	0	0.524
Female sex, %	63.6	0	0	65.2	0	0	0.143	59.2	0	0	60.9	0	0	0.615
CD4 cell count, cells/μL	155.6	1,504	17.3	163.7	1,124	15.1	0.127	193.3	11,256	61.6	186.8	9,989	56.0	0.320
Weight, kg	64.0	3,059	35.1	64.9	2,911	39.0	0.258	53.2	10,665	58.4	52.7	11,728	65.7	0.391
Hemoglobin level, g/dL	11.0	3,695	42.4	11.2	2,830	37.9	0.332	10.8	15,191	83.2	10.8	13,288	74.4	0.986

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

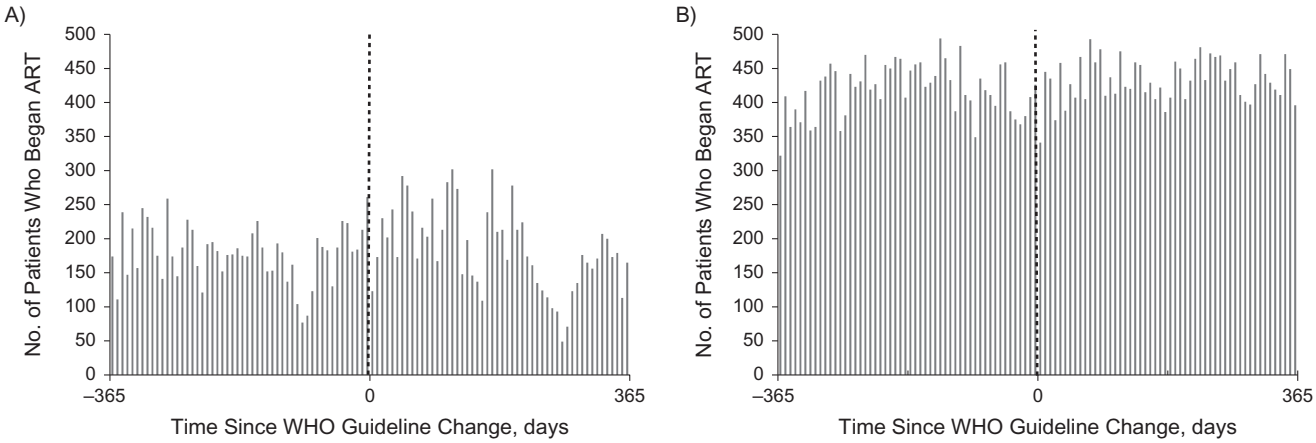

Figure 1. Number of human immunodeficiency virus–infected patients initiating antiretroviral therapy (ART), in weekly intervals, in South Africa (n = 16,179; 2010) (A) and Zambia (n = 36,115; 2007) (B) before and after the 2010 World Health Organization (WHO) guideline change recommending the use of tenofovir in first-line ART. The decrease in the number of patients initiating ART at the end of the 12-month follow-up period before and after the guideline change represents seasonal changes in the number of patients accessing care.

availability of alternate nonnucleoside reverse-transcriptase inhibitors. In South Africa, the guideline change decreased attrition by 0.9 percentage points (ITT RD = −0.9, 95% CI: −5.9, −4.1) (Figure 3) from a base of 19.8%—a relative decrease in attrition of 4.3% in the CACE. We saw a reduction in 24-month attrition of 1.8 percentage points (ITT RD = −1.8, 95% CI: −3.0, −0.12) in Zambia (Figure 4) from a base of 12.4%—a relative decrease in attrition of 15% in the CACE.

The WHO guideline change had no statistically significant impact on death (South Africa: ITT RD = 0.9 percentage points, 95% CI: −2.4, 4.1 (Figure 3); Zambia: ITT RD = −1.3 percentage points, 95% CI: −3.3, 0.8 (Figure 4)), although confidence intervals were wide. No association was observed for immunological response (South Africa: ITT RD = −6.7 cells/μL, 95% CI: −37, 24) (Figure 3); Zambia: ITT RD = −14 cells/μL, 95% CI: −42, 15 (Figure 4)) or viral load failure (South Africa: ITT RD = 2.5 percentage points, 95% CI: −0.1, 5.0 (Figure 3)) over the 24 months on ART at the threshold. After rerunning the analysis for Zambia using the July 1, 2007, date as the threshold instead of the facility-specific implementation dates, we found slightly attenuated but similar results.

Extending the analysis to 48 months in Zambia, we continued to see a decline in single-drug substitutions (RD = −2.0 percentage points, 95% CI: −4.0, −0.1) and a small decrease in attrition of 1.2 percentage points (95% CI: −3.4, 1.1)—translating to a much smaller relative reduction of 7% over 48 months of follow-up. We still saw no association with death or immune response (Web Figure 2).

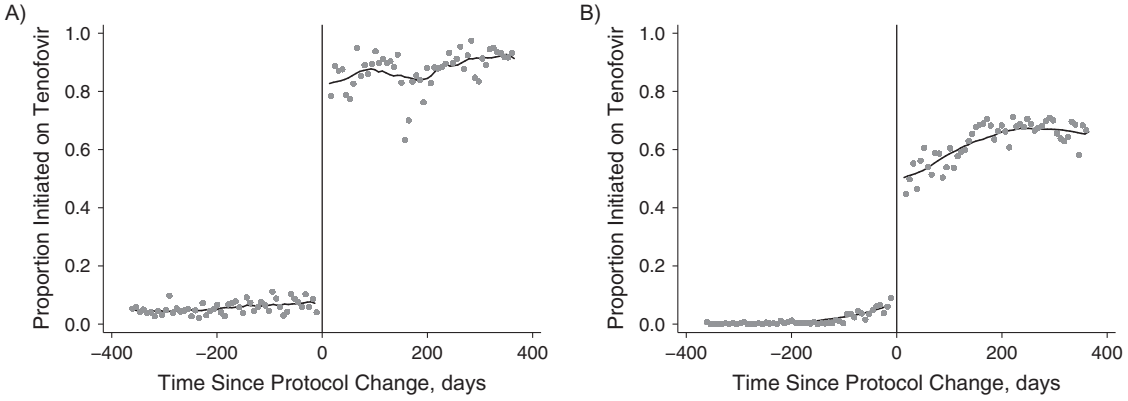

Figure 2. Probability (regression discontinuity analysis) of receiving tenofovir as first-line antiretroviral therapy among human immunodeficiency virus–infected patients in South Africa (n = 16,179; risk difference (RD) = 81.4%, 95% confidence interval: 73.3, 89.4) (A) and Zambia (n = 36,115; RD = 41.5%, 95% confidence interval: 37.6, 45.4) (B) after the 2010 change in World Health Organization guidelines, 2010 and 2007, respectively. The Imbens and Kalyanaraman (55) optimal bandwidths were 54.7 days for South Africa (A) and 104.2 days for Zambia (B). RDs were estimated at the threshold of 0. The black lines represent trends on either side of the threshold.

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

om https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

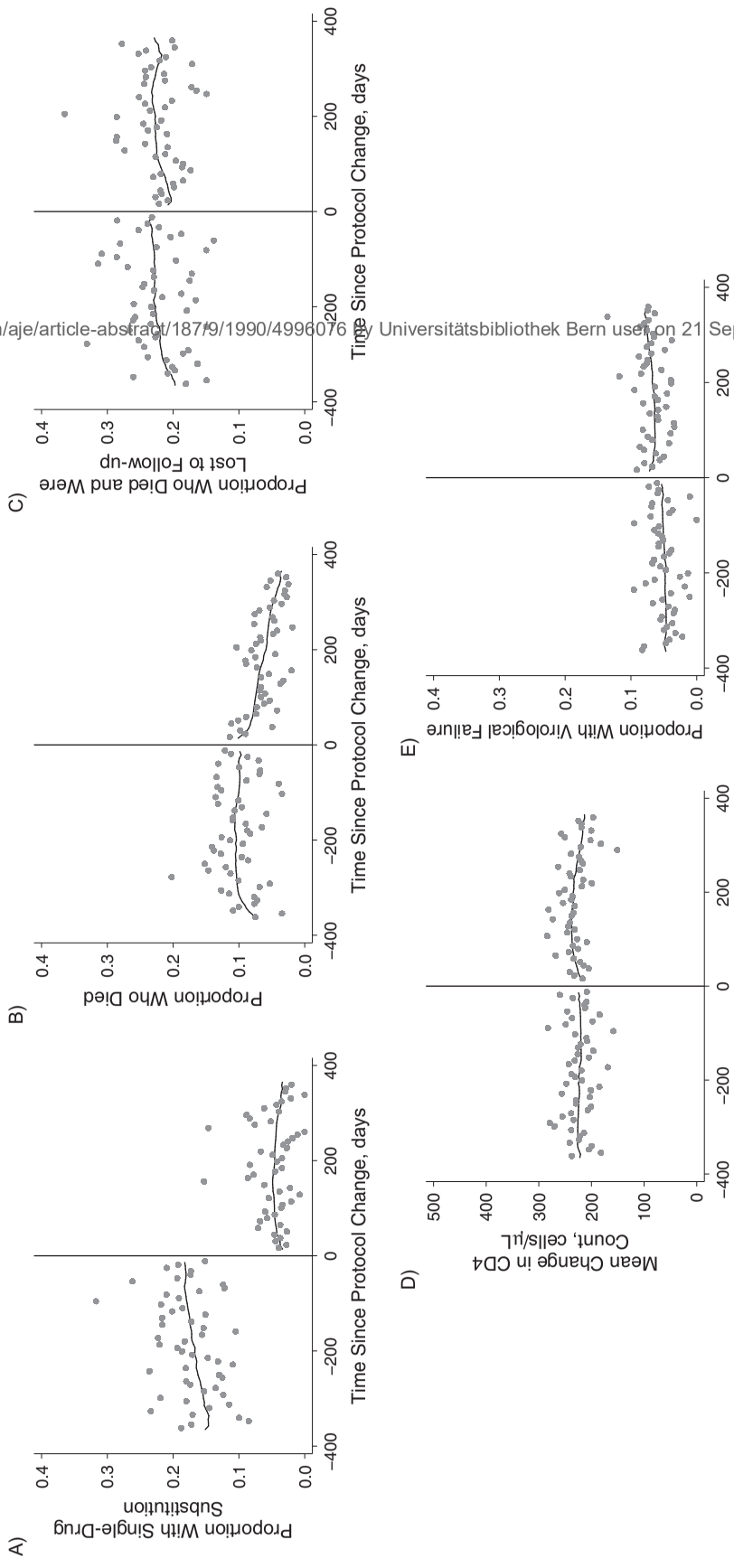

Figure 3. Results from regression discontinuity analysis of tenofovir as first-line antiretroviral therapy among human immunodeficiency virus–infected patients in South Africa ($n = 16,179$), 2010. A) Proportion of patients with a single-drug substitution (risk difference (RD) = −15.1%, 95% confidence interval (CI): −18.3, −11.9); B) proportion of patients who died (RD = 0.8%, 95% CI: −2.4, 4.1); C) proportion of patients who died and were lost to follow-up (RD = 0.8%, 95% CI: −2.4, 4.1); D) mean change in CD4 cell count from initiation of antiretroviral therapy (RD = −6.7 cells/μL, 95% CI: −37.2, 23.7); E) proportion of patients with viral load failure (RD = 2.4%, 95% CI: −0.0, 5.0) during the first 24 months in treatment. Imbens and Kalyanaraman (55) optimal bandwidths: A) proportion with single-drug substitution—163.3 days; B) proportion who died—145.2 days; C) proportion who died and were lost to follow-up—127.5 days; D) mean change in CD4 cell count—128.5 days; E) proportion with virological failure—153.2 days. RDs were estimated at the threshold of 0. The black lines represent trends on either side of the threshold.

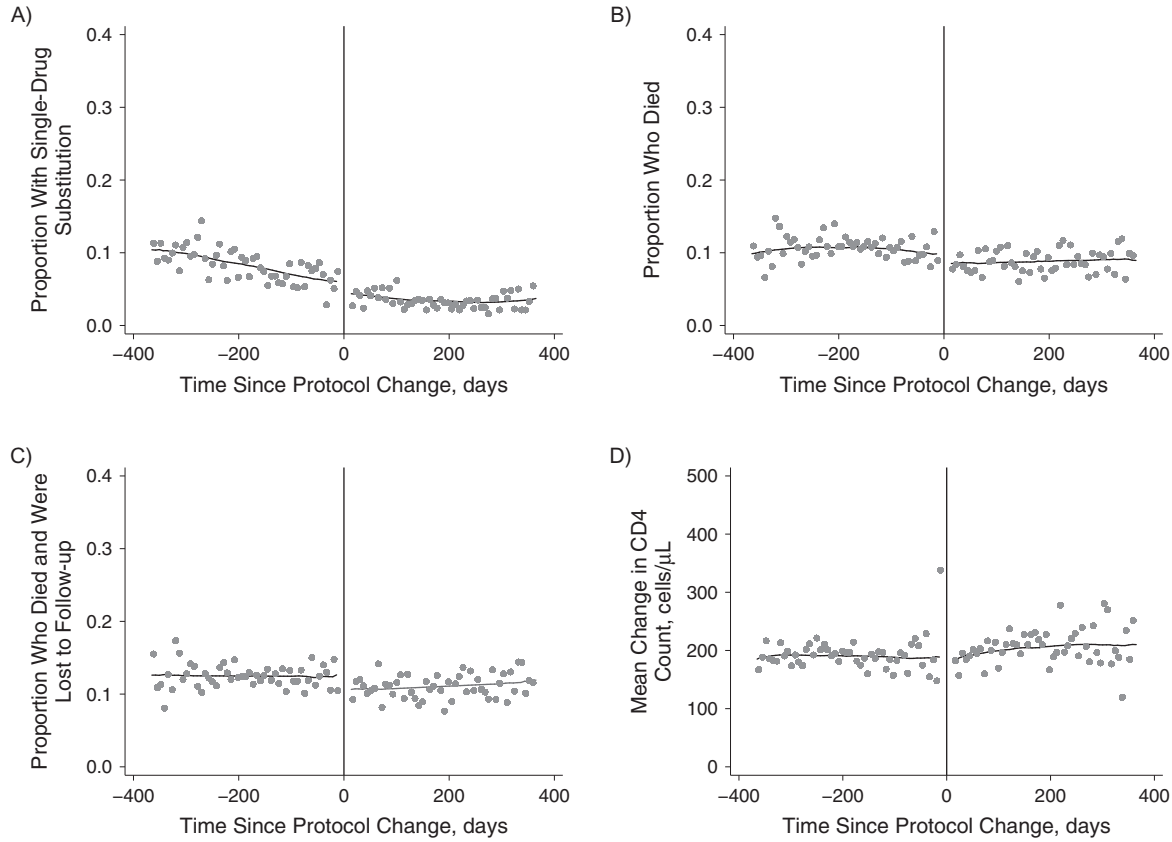

Figure 4. Results from regression discontinuity analysis of tenofovir as first-line antiretroviral therapy among human immunodeficiency virus–infected patients in Zambia (n = 36,115), 2007. A) Proportion of patients with a single-drug substitution (risk difference (RD) = −2.3%, 95% confidence interval (CI): −3.6, −0.3); B) proportion of patients who died (RD = −1.3%, 95% CI: −3.4, 0.8); C) proportion of patients who died and were lost to follow-up (RD = −1.8%, 95% CI: −3.5, −0.1); D) mean change in CD4 cell count from initiation of antiretroviral therapy during the first 24 months in treatment (RD = −13.6 cells/μL, 95% CI: −41.8, 14.6). Imbens and Kalyanaraman (55) optimal bandwidths: A) proportion with single-drug substitution—158.1 days; B) proportion who died—161.7 days; C) proportion who died and were lost to follow-up—270.8 days; D) mean change in CD4 cell count—178.3 days. RDs were estimated at the threshold of 0. The black lines represent trends on either side of the threshold.

CACE estimates

Moving from the ITT to those patients who started tenofovir because of the guideline change, the effect of initiating tenofovir on attrition in Zambia was a 4.3-percentage-point reduction (CACE RD = −1.8/0.42 = −4.3 percentage points (95% CI: −8.5, −0.3)) from a baseline level of 12.4% (95% CI: 9.9, 14.7), representing a relative reduction of 26.1% (complier relative risk = 0.74, 95% CI: 0.56, 0.98). In South Africa, the association was a 1.1-percentage-point reduction (CACE RD = −0.9/0.81 = −1.1 percentage points (95% CI: −0.7, 0.5)) in attrition from a baseline level of 19.8%, representing a relative reduction of 6.0% (complier relative risk = 0.94, 95% CI: 0.70, 1.27).

Robustness checks

The 3 robustness checks—using national rather than clinic-specific dates of policy implementation in Zambia (Web Figure 3), including patients who initiated ART within ±14 days of the policy change (Web Figure 4), and changing the bandwidth used in the linear models (Web Figures 5 and 6)—led to broadly similar results and did not change the substantive conclusions.

DISCUSSION

The 2010 WHO guidelines recommending tenofovir as the new standard of care for HIV patients were rapidly implemented in both South Africa and Zambia, leading to large and sudden increases in the proportions of patients initiating tenofovir. Although tenofovir has efficacy similar to that of stavudine, tenofovir is less toxic, and it was hoped that starting patients on tenofovir would lead to improved clinical outcomes. We have shown here that initiating tenofovir as the standard of care reduced the rate of single-drug substitution in South Africa and Zambia, consistent with a lower incidence of side effects. We also found that a policy of starting patients on tenofovir led to better retention in care over 24 months of treatment, with a 15% relative reduction in attrition in Zambia in the ITT and a 26% relative reduction for those patients actually started on tenofovir. A much smaller

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

reduction in attrition was observed in South Africa, which had a more extensive prereform policy of substituting tenofovir for stavudine if patients experienced adverse reactions to stavudine. The limited impact of the guideline change in South Africa on attrition, in spite of its rapid and thorough implementation, suggests that the prior targeted policy was effective in maintaining on ART those patients who had negative responses to the prior regimen. These findings illustrate not only the importance of addressing side effects in maintaining patients on long-term therapy but also the importance of considering treatment-effect heterogeneity in extrapolating from a target population to all patients and the limits to generalizability in different prereform contexts. Our results showed no difference in rates of death, immune response, or viral load failure.

The major strength of our study, in comparison with prior observational research on this topic, was the use of a quasi-experimental approach that generates estimates with the potential for credible causal interpretation, without strong assumptions about the absence of unobserved confounders. In particular, prior research comparing patients starting tenofovir with patients starting other regimens assumed no confounding by indication. In contrast, our regression discontinuity approach compared outcomes in 2 populations (those initiating ART just before the guideline change and those initiating it just after) that were similar in terms of both observed *and unobserved* factors, by design, and differed only with regard to the treatment available. Our analysis revealed balance with regard to observable characteristics among patients initiating ART just before and just after the guideline change, and we found no strong evidence of systematic manipulation of initiation dates. Our study had additional strengths: We conducted one of the largest analyses carried out to date on this topic. We also compared the impact of the policy change in 2 countries with different prereform standards of care, providing insight into the generalizability of the estimates.

Our study should be considered alongside its limitations. First, although attrition (including death and loss to follow-up) is observed for all patients regardless of whether they are in care, other outcomes are vulnerable to reporting bias. Due to the high rates of death—estimated at upwards of 50% (60)—among patients lost from ART programs in low- and middle-income countries, we probably underestimated mortality. As a result, our expectation is that the bias in our estimates would be towards the null, because patients at higher risk of mortality would have been less likely to be observed.

Second, measurements of CD4 cell count and viral load were conditional on retention in care. Given that the guideline change reduced attrition in Zambia, the populations remaining in care may have differed in their CD4 and viral load distributions. As with the mortality results, we interpret the results for CD4 recovery and viral failure as descriptive. However, the results for attrition have the potential to have a causal interpretation.

Third, the results of our analysis would have been confounded if patients initiating ART just before or after the guideline change differed systematically in terms of unobserved factors correlated with outcomes. In 2010, in South Africa, eligibility for ART was expanded to patients diagnosed with tuberculosis or hepatitis B virus infection at ART initiation, irrespective of CD4 cell count (36), and this could have led to a change in patient composition. We removed patients diagnosed with tuberculosis at treatment initiation from our analysis, where possible. We did not remove patients with hepatitis B virus, as testing for the virus before patients were initiated into ART was limited during the period of the study (61). There were no other major clinical policy changes coinciding with the 2010 change in guidelines. The next major WHO policy change, made after April 2010, occurred in July 2011, when the CD4 cell-count eligibility threshold for ART increased from ≤200 cells/μL to ≤350 cells/μL (62).

Fourth, the assignment variable in our study was time. As such, our study may have been at increased risk of clinicians' and/or patients' manipulating their assignment variable due to advanced knowledge of the policy change, in comparison with other studies that used strict cutoffs for assignment variables, such as CD4 cell count levels for ART eligibility (43, 63).

Fifth, there was a high proportion of missing data on observable characteristics, which may have affected our ascertainment of balance at the threshold. However, the proportions of missingness did not differ just above/below the threshold within either country, and as such we would expect the missingness to have been random at the threshold and to not have biased the results (58, 59).

Sixth, due to the lack of documentation of reasons for single-drug substitution for 90% of events among patients with the event in the cohort, we could not determine whether the substitution was due to toxicity from the drug or due to the recommendation of substituting medication in patients who were at high risk of toxicity. There is a chance that single-drug substitutions in our study were driven by the policy change and not by side effects/toxicity of stavudine. However, when assessing the association between stavudine versus tenofovir and single-drug substitution in our pediatric population, we did see a substantial spike in single-drug substitutions around the time of the guideline change as clinicians were substituting stavudine, regardless of whether the patient was tolerating stavudine well, with zidovudine or tenofovir. We believe that if substitutions were being driven by the guidelines in adults, we would have seen a similar increase, which was not present in these data.

Seventh, although we analyzed data from the largest existing collection of HIV clinical cohorts in southern Africa, our results may not be generalizable to other settings. More specifically, we have shown that reductions in drug toxicity are valuable innovations, reducing attrition from care (in Zambia) and regimen changes (in South Africa). With the scale-up of the test-and-treat strategy, patients are being asked to initiate ART earlier, often before they have experienced any serious clinical symptoms. These patients may be even more sensitive to side effects and other quality-of-life aspects of therapy. Intervening to support retention in care is critically important to maximize the clinical and population health benefit of the test-and-treat strategy.

Finally, we understand that the question regarding the association of the 2010 WHO policy change with patient outcomes has passed. Analyzing the association of the 2007 policy change in Zambia prior to the WHO policy change in 2010 would have produced valuable information for informing policy changes in other low- and middle-income countries, like South Africa. Three of the main benefits of "big data" are volume, velocity, and variety. What we were lacking in this analysis was velocity. In

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

order to answer future policy questions, we would need real-time access to observational data. With large observational HIV databases, the pooling of the data from different observational cohorts in many regions, in addition to the application and approval process, takes time and is a barrier to assessing policy changes in a timely manner.

In conclusion, pharmaceutical companies are developing a broad class of new HIV medications, seeking to reduce side effects for HIV-positive patients while maintaining the same efficacy as exists for current drugs. Little is known about the real-world clinical benefits of such innovations or the impact of scaling them up. In 2007 and 2010, respectively, Zambia and South Africa scaled up the use of tenofovir as the standard of care for first-line ART, at a significant increase in cost over existing drugs (64). We found mixed results when analyzing a natural experiment in which South Africa and Zambia replaced the use of toxic HIV drugs with similar but less toxic regimens.

On the one hand, the WHO guideline change substantially improved retention in care in Zambia, providing strong evidence that side effects lead patients to default therapy and that use of drugs without these side effects reduces attrition. These benefits point to the clinical value of such innovation: Medications with similar efficacy as current drugs, as shown in noninferiority trials, may be more effective than the status quo if they enable patients to adhere to long-term treatment regimens. On the other hand, South Africa's experience—a very large shift toward tenofovir with little to no impact on patient attrition—points to the complications of scaling up these innovations and the importance of context in generalizing findings to other settings. Prior to the guideline change, South Africa had a widely implemented targeted policy of switching patients to tenofovir if they suffered side effects. The guideline change would have eliminated months of adverse side effects for previously targeted patients—an important benefit. However, because those patients largely would have remained in care, the change in national guidelines had little association with retention for this group, even as the rate of single-drug substitutions declined precipitously. The size of this change (15 percentage points) is consistent with prior estimates of the proportion of patients with toxicity to stavudine (31–35).

With its recommendations that all patients initiate use of tenofovir, the WHO anticipated improved adherence and reduced loss to follow-up (36); this has implications for longer-term health outcomes, such as CD4 cell count recovery, viral suppression, and survival. We show that the guideline change improved retention in care in Zambia and prevented potentially months of toxicity/side effects for the 10% and 20% of patients in Zambia and South Africa, respectively, who were ultimately switched under the prior regime. Further, there may have been reductions in toxicity related to stavudine and other aspects of morbidity that were not observed in our study, which may not have led to single-drug substitutions but may have reduced quality of life for patients on ART or led to long-run adverse clinical outcomes that we did not observe. Taken as a whole, our results indicate that innovations designed to reduce side effects may improve clinical effectiveness in addition to patient quality of life in some populations. Understanding these benefits and how they vary is critical to maximizing the population impact of investments in these new drugs.

ACKNOWLEDGMENTS

Author affiliations: Department of Global Health, School of Public Health, Boston University, Boston, Massachusetts (Alana T. Brennan, Jacob Bor, Matthew P. Fox); Health Economics and Epidemiology Research Office, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa (Alana T. Brennan, Jacob Bor, Matthew P. Fox); Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts (Alana T. Brennan, Jacob Bor, Matthew P. Fox); Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa (Mary-Ann Davies, Kathryn Stinson, Andrew Boulle); Department of Health, Provincial Government of the Western Cape, Cape Town, South Africa (Andrew Boulle); Division of Public Health Medicine, School of Public Health and Family Medicine, University of Cape Town, Cape Town, South Africa (Andrew Boulle); Department of Infectious Diseases, Bern University Hospital, University of Bern, Bern, Switzerland (Gilles Wandeler); Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland (Gilles Wandeler); Division of Infectious Diseases, Department of Medicine, Tygerberg Academic Hospital, University of Stellenbosch, Cape Town, South Africa (Hans Prozesky); Kheth'Impilo AIDS Free Living, Cape Town, South Africa (Geoffrey Fatti); The Desmond Tutu HIV Centre, Institute of Infectious Disease and Molecular Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa (Robin Wood); Africa Health Research Institute, Durban, South Africa (Frank Tanser, Till Bärnighausen); School of Nursing and Public Health, University of KwaZulu-Natal, Durban, South Africa (Frank Tanser); Research Department of Infection and Population Health, University College London, London, United Kingdom (Frank Tanser); Institute of Public Health, School of Medicine, Heidelberg University, Heidelberg, Germany (Till Bärnighausen); Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, Massachusetts (Till Bärnighausen); and Center for Infectious Disease Research in Zambia, Lusaka, Zambia (Izukanji Sikazwe, Arianna Zanolini).

This work was funded by the US Agency for International Development under the terms of INROADS grant USAID-674-A-12-00029. International Epidemiology Databases to Evaluate AIDS (IeDEA)–Southern Africa is supported by the US National Institutes of Health under award number U01AI069924. J.B. was supported by the US National Institutes of Health (award 1K01MH105320-01A1). T.B. was supported by the Alexander von Humboldt Foundation through the Alexander von Humboldt Professorship (endowed by the German Federal Ministry of Education and Research), the Wellcome Trust, the European Commission, the Clinton Health Access Initiative, and the US National Institutes of Health (grant R01-HD084233 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development, grants R01-AI124389 and R01-

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

AI112339 from the National Institute of Allergy and Infectious Diseases, and grant D43-TW009775 from the Fogarty International Center).

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or the US Agency for International Development.

Conflict of interest: none declared.

REFERENCES

1. Light DW, Lexchin JR. Pharmaceutical research and development: what do we get for all that money? *BMJ*. 2012; 345:e4348.
2. Tufts Center for the Study of Drug Development. *Briefing: Cost of Developing a New Drug. November 18, 2014*. Boston, MA: Tufts University; 2014. https://www.scribd.com/document/330419323/Tufts-CSDD-Briefing-on-RD-Cost-Study-Nov-18-2014. Accessed September 1, 2017.
3. Food and Drug Administration, US Department of Health and Human Services. *Drug Approval Process*. Silver Spring, MD: US Food and Drug Administration; http://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/UCM284393.pdf. Accessed September 1, 2017.
4. Pharmaceutical Research and Manufacturers of America. *Medicines in Development for HIV 2017 Report. More Than 50 Medicines and Vaccines in Development for HIV/AIDS Infection Treatment and Prevention*. Washington, DC: Pharmaceutical Research and Manufacturers of America; 2017. http://www.phrma.org/report/medicines-in-development-for-hiv-2017-report. Accessed September 1, 2017.
5. World Health Organization. *Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection. Recommendations for a Public Health Approach*. Geneva, Switzerland: World Health Organization; 2013. http://www.who.int/hiv/pub/guidelines/arv2013/en/. Accessed October 29, 2017.
6. Uzochukwu BS, Onwujekwe OE, Onoka AC, et al. Determinants of non-adherence to subsidized anti-retroviral treatment in southeast Nigeria. *Health Policy Plan*. 2009;24(3): 189–196.
7. Monjok E, Smesny A, Okokon IB, et al. Adherence to antiretroviral therapy in Nigeria: an overview of research studies and implications for policy and practice. *HIV AIDS (Auckl)*. 2010;2:69–76.
8. La Rosa AM, Harrison LJ, Taiwo B, et al. Raltegravir in second-line antiretroviral therapy in resource-limited settings (SELECT): a randomised, phase 3, non-inferiority study. *Lancet HIV*. 2016;3(6):e247–e258.
9. Paton NI, Stöhr W, Arenas-Pinto A, et al. Protease inhibitor monotherapy for long-term management of HIV infection: a randomised, controlled, open-label, non-inferiority trial. *Lancet HIV*. 2015;2(10):e417–e426.
10. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. 2014;384(9958):1942–1951.
11. Wohl DA, Bhatti L, Small CB, et al. Simplification to abacavir/lamivudine + atazanavir maintains viral suppression and improves bone and renal biomarkers in ASSURE, a randomized, open label, non-inferiority trial. *PLoS One*. 2014; 9(5):e96187. (See erratum in *PLoS One*. 2014;9(7):e103925; dosage error in article text).
12. Nelson MR, Elion RA, Cohen CJ, et al. Rilpivirine versus efavirenz in HIV-1-infected subjects receiving emtricitabine/tenofovir DF: pooled 96-week data from ECHO and THRIVE studies. *HIV Clin Trials*. 2013;14(3):81–91.
13. Squires KE, Young B, DeJesus E, et al. ARIES 144 week results: durable virologic suppression in HIV-infected patients simplified to unboosted atazanavir/abacavir/lamivudine. *HIV Clin Trials*. 2012;13(5):233–244.
14. Gilks CF, Walker AS, Dunn DT, et al. Lopinavir/ritonavir monotherapy after 24 weeks of second-line antiretroviral therapy in Africa: a randomized controlled trial (SARA). *Antivir Ther*. 2012;17(7):1363–1373.
15. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004;292(2):191–201.
16. Arribas JR, Pozniak AL, Gallant JE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naive patients: 144-week analysis. *J Acquir Immune Defic Syndr*. 2008;47(1):74–78.
17. Velen K, Lewis JJ, Charalambous S, et al. Comparison of tenofovir, zidovudine, or stavudine as part of first-line antiretroviral therapy in a resource-limited-setting: a cohort study. *PLoS One*. 2013;8(5):e64459.
18. Bygrave H, Ford N, van Cutsem G, et al. Implementing a tenofovir-based first-line regimen in rural Lesotho: clinical outcomes and toxicities after two years. *J Acquir Immune Defic Syndr*. 2011;56(3):e75–e78.
19. Chi BH, Mwango A, Giganti M, et al. Early clinical and programmatic outcomes with tenofovir-based antiretroviral therapy in Zambia. *J Acquir Immune Defic Syndr*. 2010;54(1): 63–70.
20. Njuguna C, Orrell C, Kaplan R, et al. Rates of switching antiretroviral drugs in a primary care service in South Africa before and after introduction of tenofovir. *PLoS One*. 2013; 8(5):e63596.
21. Inzaule S, Otieno J, Kalyango J, et al. Incidence and predictors of first line antiretroviral regimen modification in western Kenya. *PLoS One*. 2014;9(4):e93106.
22. Labhardt ND, Sello M, Lejone T, et al. Adoption of new HIV treatment guidelines and drug substitutions within first-line as a measure of quality of care in rural Lesotho: health centers and hospitals compared. *Trop Med Int Health*. 2012;17(10): 1245–1254.
23. Brennan AT, Shearer K, Maskew M, et al. Impact of choice of NRTI in first-line antiretroviral therapy: a cohort analysis of stavudine vs. tenofovir. *Trop Med Int Health*. 2014;19(5): 490–498.
24. Springer SA, Friedland GH, Doros G, et al. Antiretroviral treatment regimen outcomes among HIV infected prisoners. *HIV Clin Trials*. 2007;8(4):205–212.
25. Braithwaite RS, Kozal MJ, Chang CC, et al. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. *AIDS*. 2007; 21(12):1579–1589.
26. Vo TT, Ledergerber B, Keiser O, et al. Durability and outcome of initial antiretroviral treatments received during 2000–2005 by patients in the Swiss HIV Cohort Study. *J Infect Dis*. 2008; 197(12):1685–1694.

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

27. Lodwick RK, Smith CJ, Youle M, et al. Stability of antiretroviral regimens in patients with viral suppression. *AIDS*. 2008;22(9):1039–1046.
28. Kumarasamy N, Vallabhaneni S, Cecelia AJ, et al. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. *J Acquir Immune Defic Syndr*. 2006;41(1):53–58.
29. World Health Organization. *Scaling Up Antiretroviral Therapy in Resource-Limited Settings: Treatment Guidelines for Public Health Approach. 2003 Revision*. Geneva, Switzerland: World Health Organization; 2004. http://www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf. Accessed October 29, 2017.
30. Nelson MR, Katlama C, Montaner JS, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *AIDS*. 2007;21(10):1273–1281.
31. Domingos H, Cunha RV, Paniago AM, et al. Metabolic effects associated to the highly active antiretroviral therapy (HAART) in AIDS patients. *Braz J Infect Dis*. 2009;13(2):130–136.
32. van Griensven J, Zachariah R, Rasschaert F, et al. Stavudine- and nevirapine-related drug toxicity while on generic fixed-dose antiretroviral treatment: incidence, timing and risk factors in a three-year cohort in Kigali, Rwanda. *Trans R Soc Trop Med Hyg*. 2010;104(2):148–153.
33. Murphy RA, Sunpath H, Kuritzkes DR, et al. Antiretroviral therapy-associated toxicities in the resource-poor world: the challenge of a limited formulary. *J Infect Dis*. 2007;196(suppl 3):S449–S456.
34. Ait-Mohand H, Bonmarchand M, Guiguet M, et al. Viral efficacy maintained and safety parameters improved with a reduced dose of stavudine: a pilot study. *HIV Med*. 2008;9(9):738–746.
35. Cournil A, Coudray M, Kouanfack C, et al. Reduced dose of stavudine and lipoatrophy in HIV-infected patients in Cameroon. *Antivir Ther*. 2010;15(7):1039–1043.
36. World Health Organization. *Antiretroviral Therapy for HIV Infection in Adults and Adolescents. Recommendations for a Public Health Approach. 2010 Revision*. Geneva, Switzerland: World Health Organization; 2010. http://apps.who.int/iris/bitstream/10665/44379/1/9789241599764_eng.pdf. Accessed October 29, 2017.
37. Wasti SP, Simkhada P, Randall J, et al. Factors influencing adherence to antiretroviral treatment in Nepal: a mixed-methods study. *PLoS One*. 2012;7(5):e35547.
38. Brennan AT, Maskew M, Ive P, et al. Increases in regimen durability associated with the introduction of tenofovir at a large public-sector clinic in Johannesburg, South Africa. *J Int AIDS Soc*. 2013;16:18794.
39. Cheng AK, Chen SS, Wulfsohn M, et al. 2 year long term safety profile of tenofovir DF (TDF) in treatment-experienced patients from randomized, double-blind, placebo-controlled clinical trials [poster 7.3/7]. Presented at the 9th European AIDS Conference, Warsaw, Poland, October 25–29, 2003. http://archives.who.int/eml/expcom/expcom15/applications/newmed/tenofovir/Cheng_2003_9thEurAIDSConf_Poster737_EN6137.pdf. Accessed January 1, 2018.
40. Thistlethwaite DL, Campbell DT. Regression-discontinuity analysis: an alternative to the ex-post facto experiment. *J Educ Psychol*. 1960;51(6):309–317.
41. Imbens GW, Lemieux T. Regression discontinuity designs: a guide to practice. *J Econom*. 2008;142(2):615–635.
42. Jacobson R, Zhu P, Somers MA, et al. *A Practical Guide to Regression Discontinuity*. New York, NY: MDRC; 2012. http://www.mdrc.org/sites/default/files/regression_discontinuity_full.pdf. Accessed September 1, 2017.
43. Bor J, Moscoe E, Mutevedzi P, et al. Regression discontinuity designs in epidemiology: causal inference without randomized trials. *Epidemiology*. 2014;25(5):729–737.
44. Egger M, Ekouevi DK, Williams C, et al. Cohort profile: the International epidemiological Databases to Evaluate AIDS (IeDEA) in sub-Saharan Africa. *Int J Epidemiol*. 2012;41(5):1256–1264.
45. National Department of Health, Republic of South Africa. *The South African Antiretroviral Treatment Guidelines 2010*. Pretoria, South Africa: National Department of Health; 2010. http://apps.who.int/medicinedocs/documents/s19153en/s19153en.pdf. Accessed October 29, 2017.
46. Ministry of Health, Republic of Zambia. *Adult and Adolescent Antiretroviral Therapy Protocols*. Lusaka, Zambia: Ministry of Health; 2010. http://www.who.int/hiv/pub/guidelines/zambia_art.pdf. Accessed October 29, 2017.
47. Mwinga A. Inclusion of a tenofovir-based first-line regimen in Zambia: a bold step forward? Presented at the 2007 HIV/AIDS Implementer's Meeting, Kigali, Rwanda, June 16–19, 2007.
48. Statistics South Africa. *Mortality and Causes of Death in South Africa, 1997–2003. Findings From Death Notification*. Pretoria, South Africa: Statistics South Africa; 2005. (Statistical release P0309.3). https://www.statssa.gov.za/publications/P03093/P03093.pdf. Accessed October 29, 2017.
49. Timaeus I, Dorrington R, Bradshaw D, et al. *Mortality Trends in South Africa 1985–2000: From Apartheid to AIDS*. Cape Town, South Africa: South African Medical Research Council; 2002.
50. Moscoe E, Bor J, Bärnighausen T. Regression discontinuity designs are underutilized in medicine, epidemiology, and public health: a review of current and best practice. *J Clin Epidemiol*. 2015;68(2):122–133.
51. Lee DS, Lemieux T. Regression discontinuity designs in economics. *J Econ Lit*. 2010;48(2):281–355.
52. O'Keeffe AG, Geneletti S, Baio G, et al. Regression discontinuity designs: an approach to the evaluation of treatment efficacy in primary care using observational data. *BMJ*. 2014;349:g5293.
53. Bor J, Moscoe E, Bärnighausen T. Three approaches to causal inference in regression discontinuity designs. *Epidemiology*. 2015;26(2):e28–e30.
54. Bor J, Geldsetzer P, Venkataramani A, et al. Quasi-experiments to establish causal effects of HIV care and treatment and to improve the cascade of care. *Curr Opin HIV AIDS*. 2015;10(6):495–501.
55. Imbens GW, Kalyanaraman K. Optimal bandwidth choice for the regression discontinuity estimator. *Rev Econ Stud*. 2011;79(3):933–959.
56. Imbens GW, Rubin DB. Estimating outcome distributions for compliers in instrumental variables models. *Rev Econ Stud*. 1997;64(4):555–574.
57. Abadie A. Semiparametric instrumental variables estimation of treatment response models. *J Econom*. 2003;113(2):231–263.
58. McCrary J. Manipulation of the running variable in the regression discontinuity design: a density test. *J Econom*. 2008;142(2):698–714.
59. Rubin DB. Assignment to treatment group on the basis of a covariate. *J Educ Behav Stat*. 1977;2(1):1–26.
60. Brinkhof MW, Pujades-Rodriguez M, Egger M. Mortality of patients lost to follow-up in antiretroviral treatment programmes in resource-limited settings: systematic review and meta-analysis. *PLoS One*. 2009;4(6):e5790.

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018

61. Coffie PA, Patassi A, Doumbia A, et al. Changes in viral hepatitis B screening practices over time in West African HIV clinics. Med Mal Infect. 2017;47(6):394–400.
62. World Health Organization. *Global Update on HIV Treatment 2013: Results, Impact and Opportunities*. Geneva, Switzerland: World Health Organization; 2013. http://apps.who.int/iris/bitstream/10665/85326/1/9789241505734_eng.pdf. Accessed October 29, 2017.
63. Bor J, Fox MP, Rosen S, et al. Treatment eligibility and retention in clinical HIV care: a regression discontinuity study in South Africa. *PLoS Med*. 2017; 14(11):e1002463.
64. Clinton Foundation. *Antiretroviral (ARV) Price List*. New York, NY: Clinton Foundation; 2009. http://www.givewell.org/files/DWDA%202009/Interventions/WJCF-ARVPrices-2009.pdf. Accessed September 1, 2017.

Downloaded from https://academic.oup.com/aje/article-abstract/187/9/1990/4996076 by Universitätsbibliothek Bern user on 21 September 2018