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Original Contribution

One Pill, Once a Day: Simplified Treatment Regimens and Retention in HIV Care

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Simplified drug regimens may improve retention in care for persons with chronic diseases. In April 2013, South Africa adopted a once-daily single-pill human immunodeficiency virus (HIV) treatment regimen as the standard of care, replacing a multiple-pill regimen. Because the regimens had similar biological efficacy, the shift to single-pill therapy offered a real-world test of the impact of simplified drug-delivery mechanisms on patient behavior. Using a quasi-experimental regression discontinuity design, we assessed retention in care among patients starting HIV treatment just before and just after the guideline change. The study included 4,484 patients starting treatment at a large public sector clinic in Johannesburg, South Africa. The share of patients prescribed a single-pill regimen increased by over 40 percentage points between March and April 2013. Initiating treatment after the policy change was associated with 11.7–percentage-points' higher retention at 12 months (95% confidence interval: −2.2, 29.4). Findings were robust to different measures of retention, different bandwidths, and different statistical models. Patients starting treatment early in HIV infection—a key population in the test-and-treat era—experienced the greatest improvements in retention from single-pill regimens.

fixed-dose combination treatment; HIV; instrumental variables; regression discontinuity; retention in care; single-tablet treatment; South Africa

Abbreviations: ART, antiretroviral therapy; CACE, complier average causal effect; CD4, cluster of differentiation 4; CI, confidence interval; FDC, fixed-dose combination; HIV, human immunodeficiency virus; ITT, intention-to-treat; MSE, mean squared error; RDD, regression discontinuity design; WHO, World Health Organization.

Management of human immunodeficiency virus (HIV) infection requires long-term adherence to daily medication use, similar to many other chronic conditions. Patients with poor adherence to and retention in HIV treatment are at increased risk for drug resistance (1, 2), hospitalization (3, 4), transmission (5), and mortality (6, 7). Regimen complexity may be an important barrier to treatment adherence and retention (8). Early treatment regimens involved multiple pills taken multiple times per day. Fixed-dose combinations (FDCs) combining 3 antiretroviral medications into a single daily pill were designed to lower pill-taking burdens (9) and improve adherence and retention (10).

South Africa has the largest HIV treatment program in the world, with 4 million people on antiretroviral therapy (ART) in 2019 (11). However, just half of patients who start therapy remain in care at 5 years (12). Beginning on April 1, 2013, South Africa offered FDC treatment for all HIV patients starting therapy in the country's public facilities (13). FDCs were subsequently offered to patients already established on first-line treatment (14). Dr. Ashraf Coovadia of the South African National AIDS Council highlighted the motivations for the FDC guideline change in an interview (emphasis added):

> The drugs that are combined in the FDC tablet are *neither new nor superior* to the individual drugs that we have been using. The difference is that they are *more convenient to take* in this form. Added to this convenience is the ability to take it only once per day. *We hope and expect that adherence will become better as a result of having only one pill to take* (15).

Because the biological efficacies of the FDC and multiple-pill regimens were similar, the rapid introduction of FDCs

offered a test of the hypothesis that simplified regimens can improve patient outcomes even without changes in the underlying therapeutic value of a drug.

Although taking multiple pills may seem like a small inconvenience for life-saving therapy, evidence from the behavioral economics literature suggests that small, nonmonetary "hassle" costs can have substantial effects on behavior (16–18). The challenges of multiple pill regimens may also interact with other barriers to adherence and retention, including poor mental health, substance use, inflexible work hours, migration, lack of social support, poverty, and stigma (19–21). Simplified regimens are likely to have the greatest impact on behavior for people who are not already strongly motivated to be in HIV treatment. For example, whereas ART is a matter of life and death for people with advanced HIV disease, "hassle" costs may be more salient for patients starting ART early in HIV infection, when the therapeutic benefits of ART are smaller (22, 23). Because ART virtually eliminates HIV transmission, HIV test-and-treat policies have sought to increase ART uptake, adherence, and retention early in HIV infection in order to reduce population incidence of HIV.

Using a quasi-experimental regression discontinuity design (RDD), we sought to estimate the causal effect of initiating FDC treatment, as compared with multiple pills, on clinical retention in a large public-sector HIV clinic in South Africa. Clinical trials in North America, Europe, and Australia have shown improved adherence to single-pill regimens as compared with multiple-pill regimens (9, 24, 25), and these results have been confirmed in observational studies (26–28); but few studies have evaluated causal effects of these regimens on retention in real-world, nontrial settings in sub-Saharan Africa (29). Understanding the value of single-pill FDC regimens in real-world settings has implications for treatment guidelines and investments in pharmaceutical innovation to reduce regimen complexity—for HIV as well as for other manageable chronic conditions.

METHODS

Data and study population

The study population included treatment-naive adult patients (ages 16 years or older) initiating first-line ART from September 1, 2011 to August 31, 2014, at Themba Lethu Clinic, a large outpatient public-sector HIV treatment clinic in Johannesburg, South Africa (30). Information on patient demographic characteristics, laboratory results, prescriptions, visit history, clinical conditions, and follow-up status (in care, died, lost to follow-up, or transferred) was captured at each clinical encounter in an electronic medical record called TherapyEdge-HIV (Advanced Biological Laboratories S.A./TherapyEdge Inc., Luxembourg City, Luxembourg). After initiating ART, patients had medical follow-up visits at months 1, 3, 6, and 12, and annually thereafter. Viral loads were measured at 6 and 12 months and annually thereafter, until 2013, when the 12-month measure was eliminated. Patients returned to the clinic to pick up ART medications monthly for the first 6–12 months of treatment and every 2 months thereafter, once stable (30).

Pharmacy dispensing data were recorded in a separate electronic system and were available for September 2012–October 2014. Data on prescription date, regimen, brand name, and dosing instructions were used to determine the patient's first treatment regimen. Beginning on April 1, 2013, single-tablet FDCs of tenofovir/emtricitabine/efavirenz were recommended as first-line treatment (14), replacing a prior regimen which included 3 pills, once per day, of tenofovir, lamivudine or emtricitabine, and efavirenz or nevirapine (13).

All patients were followed up for at least 1 year. Throughout the study period, patients were eligible for ART if they had 1) a cluster of differentiation 4 (CD4)-positive (CD4+) cell count less than or equal to 350 cells/μL or 2) a CD4+ cell count greater than 350 cells/μL and World Health Organization (WHO) stage 4 disease (31). Eligibility was extended to patients with WHO stage 3 disease on April 13, 2013. Because this change coincided with the FDC policy, we excluded patients with CD4+ cell counts greater than 350 cells/μL and WHO stage 3 disease ($n = 17$ patients), who would have been ART-eligible only in the postpolicy period. We additionally excluded pregnant women and patients with tuberculosis (32, 33) and patients whose regimen could not be ascertained from pharmacy data ($n = 125$).

Study design

We performed a regression discontinuity analysis (34, 35) to assess whether starting ART in the FDC era affected retention in treatment. We compared outcomes among patients who initiated ART immediately before the guideline change and those who initiated it immediately afterward. Under the assumption that dates of ART initiation are as-good-as-randomly assigned, patients initiating ART before and after the policy change were similar, on average, with respect to observed and unobserved characteristics, similar to a randomized trial. Differences at the threshold are interpretable as intention-to-treat (ITT) effects of the policy change. The policy change can also be used as an instrumental variable to estimate the effect of starting FDC vis-à-vis multiple pills.

Exposure and outcome assessment

Our primary measure of attrition was lapse in care within the first year of treatment, defined as any ≥4-month period with no clinical visits or ART pickups. This included short-term gaps as well as deaths, losses to follow-up, and transfers for patients with final visits within the first 12 months of treatment (with follow-up until 16 months to detect the 4-month gap). To assess robustness to different definitions of retention, we also examined risks of not being in care 1 year after initiation (no visits at 12–16 months), long-term attrition (≥3-year absence from care starting in the first year), and no 6-month viral load testing (4–10 months) as a laboratory-based proxy for retention in ART. For all outcomes, mortality was included as loss to follow-up.

Our primary exposure was whether the patient starting ART was prescribed an FDC or multiple-pill regimen ("regimen type"). Regimen type was not universally documented in clinical notes (52% missing) or pharmacy records (5%

missing). We classified patients as starting FDC if either source indicated an FDC regimen. We assumed that patients who initiated ART prior to the September 2012 availability of pharmacy data were prescribed multiple pills, since FDCs were not yet available. We used date of ART initiation as the assignment variable in the RDD, with patients starting on April 1, 2013, or later exposed to the new guidelines.

Statistical analysis

We estimated the association between starting ART after the FDC policy change and retention in care in regression discontinuity models, following RDD best practices. We modeled the relationship between the assignment variable (date of initiation) and outcomes using local linear regression models, allowing for an intercept shift at the threshold (April 1, 2013) and separate slopes on either side of the threshold. We limited our analyses to patients who started ART within a bandwidth around the threshold and used a triangular kernel to place greater weight on observations closer to the threshold (36, 37). We selected the bandwidth using a data-driven algorithm that minimizes the mean squared error (MSE) of the RDD treatment effect estimator, balancing the fit of the model (less bias with smaller bandwidths) against precision (lower variance with larger bandwidths) (37–39). Point estimates and robust bias-corrected 95% confidence intervals (CIs) were calculated using the "rdrobust" command in Stata (StataCorp LLC, College Station, Texas) (39). In sensitivity analyses, we reran our analyses using bandwidths of 50% and 200% of the MSE-optimal bandwidth and with a rectangular kernel. Linear probability models offer an intuitive risk-difference interpretation and perform well when the predicted probability is not close to 0 or 1. We used logistic regression models in sensitivity analyses.

RDDs yield valid causal inferences if patients starting ART just before/after April 2013 are truly similar. Causal inference may be jeopardized if ART starting dates were manipulated—for example, if select patients were deliberately "held back" to initiate ART after the policy change. We assessed for systematic manipulation using the McCrary density test (40), comparing the number of patients starting ART just before the policy change with those starting ART just after the policy change. We also assessed the similarity of patients starting ART just before/after the policy change with respect to measured covariates. Assessing similarity in baseline covariates at the threshold serves the same purpose as a balance table in a randomized clinical trial, building confidence that the treatment was in fact as-good-as-randomly assigned. We also evaluated the potential for bias due to missingness in pharmacy data used to classify regimen type, comparing completeness of dispensing records before and after the policy change. In addition, we assessed for changes in dosing that could have led to mismeasurement of retention on different regimens.

Our primary analysis assessed the ITT effect of starting treatment after the policy change. We note that this ITT effect was diluted by the presence of patients who started multiple-pill regimens even after the policy change ("never takers") and a small share of patients who started FDC ahead of the policy change ("always takers"). Because these patients' treatment regimens were not affected by their ART starting date, we expected no difference in attrition for these groups. In order to estimate the causal effect of regimen type actually prescribed, we fitted "fuzzy" RDD models, using the April 2013 policy change as an instrument for whether the patient started FDC. Under additional assumptions of excludability and monotonicity (see the Web Appendix, available at https://doi.org/10.1093/aje/kwac006), this analysis estimates a complier average causal effect (CACE)—that is, the causal effect of being prescribed FDC on attrition among "compliers," those patients who were prescribed FDC because of the guideline change. We used the "rdrobust, fuzzy()" routine in Stata (37) to estimate the CACE, with a single MSE-optimal bandwidth jointly selected for the combined model, accounting for bias and precision in both the first-stage and ITT estimates. We report robust, bias-corrected 95% CIs for the CACE (39, 41).

We hypothesized that the impact of FDC on retention would be larger for treatment initiators who were in better health. We therefore stratified our analyses by baseline patient health: CD4+ cell count (0–199 cells/μL or ≥200 cells/μL), WHO clinical stage (stage 1 or 2, representing early-stage HIV disease, vs. stage 3 or 4, representing later-stage HIV disease), and anemia status (hemoglobin concentration <13 g/dL for men and <11.5 g/dL for women). We also stratified by sex (male/female) and age at treatment initiation (16–29, 30–39, 40–49, or ≥50 years).

RESULTS

Cohort characteristics

The study population included 4,626 patients who initiated first-line ART between September 2011 and August 2014, prior to exclusion of patients with CD4+ cell counts greater than 350 cells/μL and WHO stage 3 disease, pregnant women, and patients with tuberculosis (n = 142). After exclusions, our analysis included 4,484 patients, of whom 1,121 started ART within 180 days of the guideline change. Around the time of the policy change (±180 days), the population of patients initiating treatment at Themba Lethu was 43% male, with a mean age of 38.5 (standard deviation, 9.9) years and a mean CD4+ cell count of 192.8 (standard deviation, 162.2) cells/μL. Forty-five percent of patients were anemic, and 14% presented with WHO stage 3 or 4 disease (Table 1). Of 1,281 patients initiating a single-treatment FDC regimen, 98.6% were prescribed tenofovir/emtricitabine/efavirenz. Of the 3,203 patients prescribed multiple-pill regimens, treatments included tenofovir/lamivudine/efavirenz (79.0%), stavudine/lamivudine/efavirenz (12.6%), tenofovir/lamivudine/nevirapine (4.6%), tenofovir/emtricitabine/efavirenz (2.8%), and stavudine/lamivudine/nevirapine (1.0%).

Initiation of patients on a single-tablet FDC regimen

We observed a clear shift from multiple-pill regimens to single-pill regimens after April 1, 2013 (Figure 1, Web Figure 1, Table 1), with the policy leading to an immediate 41.8–percentage-point (95% CI: 19.3, 57.3) increase in the

Table 1. Baseline Characteristics of Patients Initiating Antiretroviral Therapy for HIV Infection at Themba Lethu Clinic ≤180 Days Before and After the Policy Change Recommending Use of Fixed-Dose Combination Treatment Regimens, Johannesburg, South Africa, 2011–2014

Baseline Characteristic or ART Regimen	Total (n = 1,121)		≤180 Days Before Policy Change (n = 598)		≤180 Days After Policy Change (n = 523)		Difference Associated With Policy Change[a]		
	No.	%	No.	%	No.	%	RDD Estimate, PP[b]	95% CI	Bandwidth[c], days
Male sex	487	43.4	252	42.1	235	44.9	2.2	−10.5, 17.5	±216
Age at treatment initiation, years[d]	38.5 (9.9)		38.6 (9.5)		38.5 (10.3)		−1.8	−5.1, 1.3	±171
CD4+ cell count at baseline, cells/μL[d]	192.8 (162.2)		196.2 (163.1)		188.8 (161.2)		−25.6	−99.0, 36.2	±135
Anemia at baseline	500	44.6	270	45.2	230	44.0	8.9	−7.2, 25.0	±149
WHO stage ≥3	155	13.8	81	13.5	74	14.1	3.6	−7.9, 15.6	±142
Received FDC regimen	463	41.3	15	2.5	448	85.7	41.8	19.3, 57.3	±70

Abbreviations: ART, antiretroviral therapy; CI, confidence interval; FDC, fixed-dose combination; HIV, human immunodeficiency virus; MSE, mean squared error; PP, percentage points; RDD, regression discontinuity design; WHO, World Health Organization.

[a] The bandwidth is the window of data around the threshold that was used to generate the RDD estimate. For each outcome, an MSE-optimal bandwidth was computed using the "rdrobust" command in Stata (37).

[b] Values presented are PP unless otherwise indicated.

[c] Calculated using local linear regression with an MSE-optimal bandwidth, a triangular kernel, and robust, bias-corrected 95% CIs. The model included separate slopes on either side of the threshold and a shift in intercept at the threshold, which is the risk difference associated with the policy.

[d] Values are expressed as mean (standard deviation) and difference in mean values at the time of the policy change.

Figure 1. Monthly proportion of all patients initiating standard first-line antiretroviral therapy at Themba Lethu Clinic who were prescribed a single-pill regimen, Johannesburg, South Africa, 2011–2014. Dots represent monthly percentages; lines represent local linear regression models with a 70-day bandwidth and a triangular kernel. FDC, fixed-dose combination.

share of patients starting FDC and further increases thereafter. Overall, FDC was prescribed to 2.5% of patients in the 6 months before the policy change and 85.7% of patients in the 6 months after the policy change (Table 1), an increase of 83.2 percentage points in the percentage of patients starting FDC.

Evidence for the validity of the design

The McCrary density test found no evidence that ART starting dates were manipulated (Web Figure 2). Regression discontinuity models revealed that patients starting ART just before and just after the guideline change were similar with regard to baseline covariates, consistent with the quasi-random assignment of ART starting dates in the neighborhood around the threshold (Table 1, Web Figure 3). A comparison of monthly treatment type distribution (FDC vs. multiple pills) from clinic records versus pharmacy data showed similar distributions over time from the 2 data sources (Web Figure 4), suggesting that completeness of pharmacy records did not differ by regimen type. Further, we observed no notable change in the number of pharmacy pickups among patients remaining in care (Web Figure 5), implying that the quantity of daily doses dispensed at one pickup was the same for multiple-pill and FDC regimens. These findings support causal attribution of differences in outcomes at the threshold to the FDC policy.

Effects of the FDC policy change on retention in care

Table 2 presents ITT estimates of the impact of the FDC policy change on patient retention. Our primary outcome—the number of patients experiencing a ≥4-month gap in care—dropped from 38.3% to 26.5% (−11.7 percentage points; 95% CI: −29.4, 2.2) among patients starting

Table 2. Regression Discontinuity Results for Attrition Outcomes Associated With the April 1, 2013, Switch to Fixed-Dose Combination Treatment as Standard First-Line Antiretroviral Therapy for HIV at Themba Lethu Clinic, Johannesburg, South Africa, 2011–2014

Outcome	Intention-to-Treat Effect[a]					Complier Average Causal Effect[b]		
	Bandwidth[c], days	Predicted %		RD	95% CI	Bandwidth[c], days	RD	95% CI
		Just *Before* April 1, 2013	Just *After* April 1, 2013					
≥4-month gap in care during first year	±147.0	38.3	26.5	−11.7	−29.4, 2.2	±129.6	−21.7	−54.7, 2.1
Absent from care at 1 year	±143.5	31.0	19.4	−11.6	−28.1, 1.0	±130.4	−19.9	−49.7, 1.9
Long-term attrition by 1 year	±146.3	29.4	16.8	−12.6	−28.2, −0.8	±127.4	−21.6	−51.1, −0.1
No 6-month viral load monitoring	±193.3	34.4	19.0	−15.5	−28.9, −2.5	±119.2	−27.7	−58.8, −0.7

Abbreviations: CI, confidence interval; ITT, intention-to-treat; MSE, mean squared error; RD, risk difference.

[a] ITT effects were estimated using the "rdrobust" command in Stata (37), with an MSE-optimal bandwidth based on a triangular kernel. The 95% CIs are robust, bias-adjusted CIs.

[b] The complier average causal effect was estimated with the "rdrobust, fuzzy()" command in Stata (37), using the same MSE-optimal bandwidth for the first- and second-stage equations. The corresponding ITT effect and first-stage models are displayed in Web Table 1.

[c] The bandwidth is the window of data around the threshold that was used to generate the regression discontinuity design estimate. For each outcome, an MSE-optimal bandwidth was computed using the "rdrobust" command in Stata (37).

treatment before the policy change versus after the policy change. Absence from care at 1 year decreased from 31.0% to 19.4% (−11.6 percentage points; 95% CI: −28.1, 1.0), long-term attrition by 1 year decreased from 29.4% to 16.8% (−12.6 percentage points; 95% CI: −28.2, −0.8), and noncompliance with 6-month viral load monitoring decreased from 34.4% to 19.0% (−15.5 percentage points; 95% CI: −28.9, −2.5). Plots of our primary outcome (Figure 2) and secondary outcomes (Figure 3) illustrate the differences in attrition with the policy change.

Effects of starting FDC among "compliers"

The ITT effect of the policy change underestimates the effect of being prescribed FDC on retention in care, because not all patients were prescribed FDC after the policy change. We estimated CACEs by scaling the ITT by the share of patients who were prescribed FDC because of the policy. Our CACE estimates revealed that being prescribed an FDC instead of multiple pills led to a 21.7–percentage-point decrease in 4-month gaps in care (95% CI: −54.7, 2.1), a 19.9–percentage-point decrease in absence from care at 1 year (95% CI: −49.7, 1.9), a 21.6–percentage-point decrease in long-term attrition by 1 year (95% CI: −51.1, −0.1), and a 27.7–percentage-point decrease in missed 6-month viral load tests (95% CI: −58.8, −0.7) (Table 2, Web Table 1).

Subgroup analyses

We then stratified our CACE analyses to understand the effect of FDCs on attrition in clinic subpopulations (Table 3). Percentage-point reductions in attrition were largest for patients with higher CD4+ cell counts (≥200 cells/μL) (percentage-point change = −56.7, 95% CI: −122.5, −14.2), patients with early clinical disease (WHO stage 1 or 2) (percentage-point change = −23.2, 95% CI: −53.7, −5.1), nonanemic patients (percentage-point change = −26.2, 95% CI: −67.4, 2.1), and women (percentage-point change = −26.2, 95% CI: −62.9, −2.8).

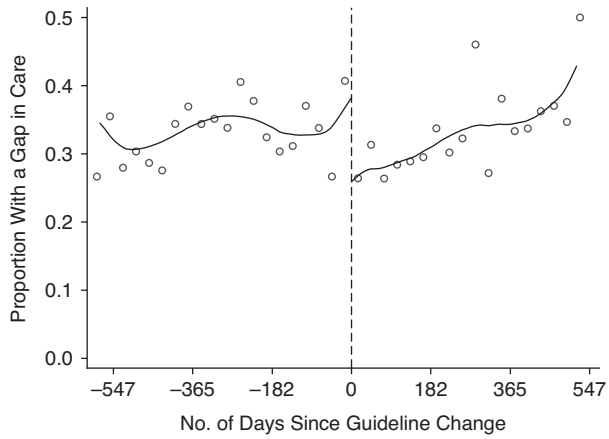

Figure 2. Proportion of patients with a 4-month gap in care among patients starting antiretroviral therapy before and after the switch to a single-pill regimen, Themba Lethu Clinic, Johannesburg, South Africa, 2011–2014. Dots represent monthly percentages; lines represent local linear regression models with a bandwidth of 147.0 days and a triangular kernel.

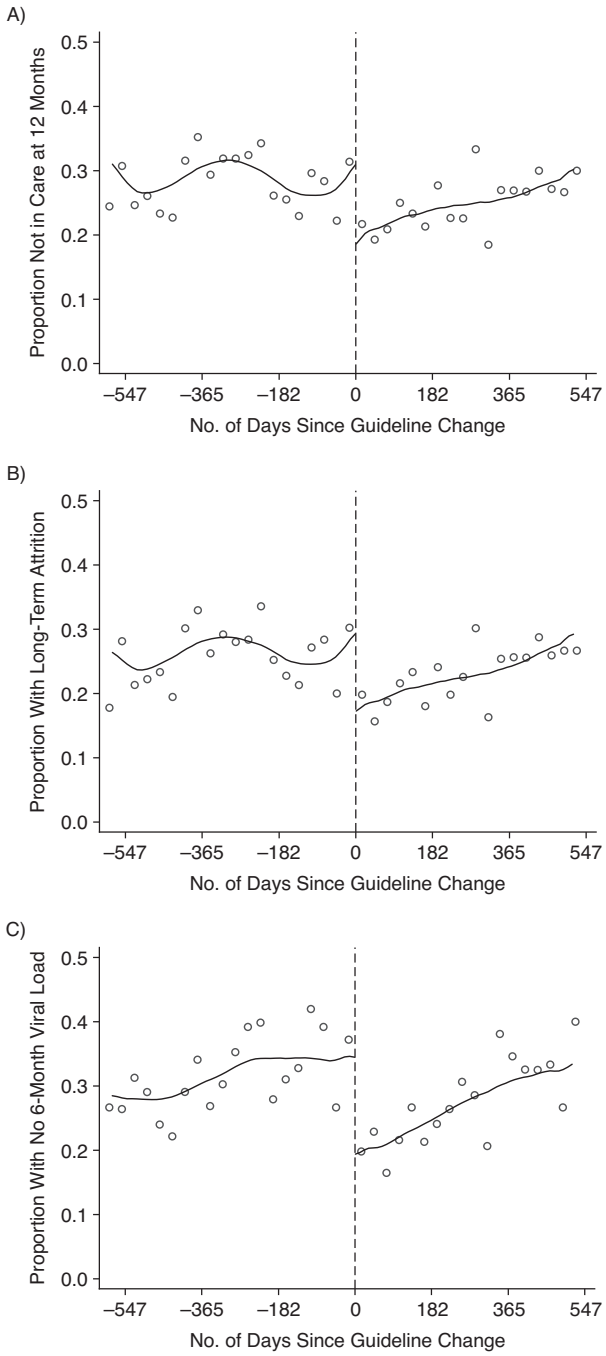

Figure 3. Secondary attrition outcomes among patients who initiated antiretroviral therapy at Themba Lethu Clinic in Johannesburg, South Africa, 2011–2014. A) Absence from care at 1 year; B) long-term attrition by 1 year; C) failure to have a 6-month viral load measurement. Dots represent monthly percentages; lines represent local linear regression models with bandwidths of 143.5 days (A), 146.3 days (B), and 193.3 days (C) and a triangular kernel.

Sensitivity analyses

Results were robust to changes in the bandwidth (Web Table 2) and kernel and to the use of logistic regression in lieu of the linear model (Web Figure 6).

DISCUSSION

We investigated the impact of "1 pill, once-a-day" HIV treatment on patient retention in South Africa's public-sector HIV program. Using an RDD, we exploited the rapid shift from multiple-pill regimens to single-pill FDC for new patients. We estimated that 1-year attrition was 11.7 percentage points lower (38.3% vs. 26.5%) among patients who initiated ART after the introduction of FDC. Among "compliers," patients whose regimen type was determined by the policy change, starting FDC reduced attrition by 21.7 percentage points. Although the 95% confidence intervals indicated a wide range of possible parameter values, our point estimates were consistent across different measures, including measures relying on different underlying data sources (laboratory results vs. clinic visits), and were robust to different bandwidths and regression specifications.

Prior studies have compared adherence to single-tablet regimens versus multiple-tablet regimens, with most investigators reporting higher adherence for single-tablet regimens (9, 24–26, 28, 29, 42–46). However, the majority of these studies were conducted in North America and Western Europe, with limited generalizability to sub-Saharan Africa, and most did not assess retention as an outcome. To our knowledge, this was the first study to evaluate real-world retention impacts of single-pill ART in sub-Saharan Africa using a causally robust RDD study design (47–50).

Our subgroup analyses revealed strong associations between starting a single-pill FDC and retention among healthier patients—that is, those with a CD4+ cell count greater than or equal to 200 cells/μL, no anemia, and no stage 3 or 4 HIV illness—and no association among sicker patients. Patients who have not yet experienced advanced HIV illness may lack motivation to be on ART (23). Our data suggested that the reduction in "hassle" costs associated with FDC had the greatest impact on ART retention in this population. With countries seeking to expand ART coverage among healthy patients via test-and-treat policies, eliminating hassle costs such as regimen complexity may play an even more important role in supporting adherence and retention going forward.

We also found effect modification by sex, with large estimated effects among women and no estimated effect among men. Men face many barriers to HIV testing and care-seeking (51, 52) and tend to seek care later in disease progression (53). Whereas men often delay care-seeking until they experience HIV-related symptoms, women are often diagnosed with HIV and started on ART as part of routine reproductive health care. Because many women enter HIV care without ever actually seeking out HIV care, women may be more likely than men to be "on the fence" about treatment and therefore more likely to be impacted by a small reduction in hassle costs. We note that this interpretation is not inconsistent with the high rates of attrition documented among men (54), which could indicate that men face other large obstacles to staying on ART that are not addressed by simplified drug regimens.

Our findings have implications for the therapeutic management of HIV and other chronic diseases. First, our results suggest that simplified regimens have benefits for patients,

Table 3. Stratified Regression Discontinuity Design Estimates of the Effect of Single-Pill Fixed-Dose Combination Treatment for HIV (Compared With Multiple Pills) on the Risk of a 4-Month Gap in Care Within the First Year of Treatment, 2011–2014

Stratifying Variable	Complier Average Causal Effect[a]		
	Bandwidth[b], days	RD	95% CI
Overall	±129.6	−21.7	−54.7, 2.1
Sex			
Male	±128.2	−3.4	−45.3, 35.7
Female	±174.3	−26.2	−62.9, −2.8
Age, years			
16–29	±191.1	−23.8	−66.7, 21.2
30–39	±264.0	−14.1	−47.1, 9.3
40–49	±125.9	−18.5	−72.8, 28.0
≥50	±171.7	−19.5	−88.8, −1.6
Anemia			
Yes	±222.0	−6.3	−32.7, 20.8
No	±156.3	−26.2	−67.4, 2.1
WHO stage			
3 or 4	±141.8	15.9	−66.2, 100.8
1 or 2	±166.6	−23.2	−53.7, −5.1
CD4+ cell count, cells/μL			
0–199	±238.7	5.8	−16.5, 28.7
≥200	±135.4	−56.7	−122.5, −14.2

Abbreviations: CD4, cluster of differentiation 4; CI, confidence interval; MSE, mean squared error; RD, risk difference; WHO, World Health Organization.

[a] The complier average causal effect was estimated using the "rdrobust, fuzzy()" command in Stata (37), with a triangular kernel and the same MSE-optimal bandwidth for the first- and second-stage equations. The 95% CIs are robust, bias-adjusted CIs.

[b] The bandwidth is the window of data around the threshold that was used to generate the regression discontinuity design estimate. For each outcome, an MSE-optimal bandwidth was computed using the "rdrobust" command in Stata (37).

complementing recent evidence that less toxic regimens also improve retention (49). Messaging on the relative convenience and tolerability of modern ART regimens might increase treatment uptake as South Africa strives to end the HIV epidemic. Second, as our study illustrates, simplified regimens can be scaled up very quickly through changes in guidelines and centralized procurement, without requiring changes in patient or health-care provider behavior. In this, FDC contrasts with other retention interventions such as case management and adherence clubs. Third, our findings suggest that pharmaceutical innovations to simplify complex drug regimens could have substantial public health benefit.

Our study had several limitations. First, we were unable to determine why FDCs improved retention. Greater patient satisfaction (55) and improved quality of life (56) have been attributed to FDCs in prior studies. The most commonly prescribed FDC and the leading multipill regimen at the time had similar biological efficacy and similar risks of side effects (57). Thus, it is likely that the observed increase in retention was related to the lower pill burden rather than to any change in the efficacy or tolerability of treatment. Second, FDC was rolled out at the same time ART eligibility was extended to patients with stage 3 illness and CD4+ cell counts greater than 350 cells/μL. All such patients were excluded from the analysis. However, increased facility congestion could have contributed to the continuous rise in background attrition rates during the study period. Third, while we are unaware of other contemporaneous changes to clinical procedures, our results might be biased if the introduction of FDC led to an overall focus on improving initiation procedures for patients starting on the new regimen. Fourth, as with all clinical cohorts observed through routine data, gaps in record-keeping could have led us to underestimate retention. Our use of multiple definitions of retention provides confidence that our results were not sensitive to 1 specific definition. Although overall retention may have been underestimated, there is no reason to believe that there would be different patterns of missingness in clinical records for patients starting just before the FDC policy implementation date versus just after the FDC policy date. Patients starting just before/after the policy change had follow-up that overlapped nearly completely and experienced nearly

identical conditions at the clinic; the only difference was that patients starting ART just after the policy change were much more likely to start FDC. Fifth, while we found reduced attrition among patients starting single-pill ART, it is unknown whether our results would be generalizable to patients who were already established on multiple-pill regimens and were switched to FDC.

In summary, starting patients on "1 pill, once-a-day" ART increased retention in HIV care at a large public-sector clinic in South Africa. Simplified treatment regimens can improve the real-world management of chronic diseases in low-resource settings.

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Replication data and the Stata.do file are available on GitHub (58).

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