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Tenofovir stock shortages have limited impact on clinic- and patient-level HIV treatment outcomes in public sector clinics in South Africa

Alana T. Brennan[1,2,3], Jacob Bor[1,2], Mary-Ann Davies[4], Francesca Conradie[5], Mhairi Maskew[2], Lawrence Long[2], Ian Sanne[1,2,5,6] and Matthew P. Fox[1,2,3]

1 *Department of Global Health, Boston University School of Public Health, Boston, MA, USA*
2 *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*
3 *Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA*
4 *Centre for Infectious Disease Epidemiology and Research, Cape Town, South Africa*
5 *Clinical HIV Research Unit, University of the Witwatersrand, Johannesburg, South Africa*
6 *Right to Care, Johannesburg, South Africa*

Abstract

OBJECTIVE Using data from four public sector clinics in South Africa, we sought to investigate provider- and patient-level outcomes, to understand how the 2012 tenofovir stock shortage affected the HIV care and monitoring of ART patients.

METHODS Prospective cohort analysis of ART-naïve, non-pregnant, HIV-infected patients >18 years initiating first-line ART between 1 July 2011–31 March 2013. Linear regression was used for all outcomes (number of ART initiates, days between pharmacy visits, transfers, single-drug substitutions, treatment interruptions, missed pharmacy visits, loss to follow-up and elevated viral load). We fit splines to smooth curves with knots at the beginning (1 February 2012) and end (31 August 2012) of the stock shortage and displayed results graphically by clinic. Difference-in-difference models were used to evaluate the effect of the stock shortage on outcomes.

RESULTS Results suggest a potential shift in the management of patients during the shortage, mainly fewer average days between visits during the shortage *vs.* before or after at all four clinics, and a significant difference in the proportion of patients missing visits during *vs.* before (RD: 1.2%; 95% CI: 0.5%, 2.0%). No significant difference was seen in other outcomes.

CONCLUSION While South Africa has made great strides to extend access to ART and increase the quality of the health services provided, patient care can be affected when stock shortages/outs occur. While our results show little effect on treatment outcomes, this most likely reflects the clinics' ability to mitigate the crisis by continuing to keep patient care and treatment as consistent as possible.

keywords antiretroviral therapy, stock-outs, stock shortages, low- and middle-income countries, patient outcomes, clinic outcomes

Introduction

Rapid expansion of antiretroviral therapy (ART) for treatment of HIV in low- and middle-income countries (LMICs) has been achieved using a 'public health approach' that prioritises standardised treatment regimens purchasable in large quantities and delivered at scale [1]. As WHO expands eligibility criteria for HIV care and treatment to larger populations in LMICs, the expectation is that programmes will grow and become more reliant on large bulk purchases and bureaucracies, increasing the chances of breakdowns and interruptions in healthcare delivery in already overburdened health care systems.

Since the roll-out of ART in sub-Saharan Africa, there have been reports of stock shortages (i.e. having less stock of a medicine available in the facility than required for patients until the next order is received [2]) and stock-outs (i.e. having no stock of a medicine which was required for patient use in that facility [2]) [2–6]. Despite being one of the wealthiest countries on the continent, South Africa has been no exception. South Africa has the largest number of people living with HIV, estimated at 5.8 million, and by far the largest number of people on ART in the world (3.2 million by the end of 2014) [7]. In February 2012, a stock shortage of tenofovir occurred and lasted for roughly 7 months [2]. At the time of the

shortage, clinicians were advised to place patients on stavudine or zidovudine, unless they had contraindications to the drugs, instead of tenofovir [8]. The expectation was that patients initiated on or switched to the older NRTIs (stavudine or zidovudine) during the stock shortage would substitute with tenofovir when it became available. During this time, 20% of health facilities throughout South Africa were estimated to have had either a stock shortage or stock-out of tenofovir [2], the consequences of which have not been quantified to date.

Previously published work in quantifying the effect of stock shortages or stock-outs on treatment outcomes in LMICs is scarce, as the few existing studies were either conducted early on in treatment roll-out before a consistent supply of antiretrovirals (ARVs) had been established [3, 4] or during times of conflict [5]. A more recent study from Cote D'Ivoire reported ART stock-outs of less common ARV drugs (combivir – a fixed-dose combination nucleoside reverse transcriptase inhibitor (NRTI) and nevirapine – a non-nucleoside reverse transcriptase inhibitor (NNRTI)), affecting more than 10% of HIV-positive patients on treatment in their cohort, which doubled the risk of interruptions in care and death [6].

There are many mechanisms, at the level of the provider and the patient, through which a stock shortage or stock-out could affect HIV treatment outcomes. During a stock shortage or stock-out of ARV drugs, care and treatment of patients could remain unaffected if providers had other drug options in stock to mitigate the circumstances until the shortage was resolved. In this scenario, treatment-experienced patients and treatment-naïve patients could be switched to or initiated on older but effective [9, 10] ARV drugs until the shortage ended. The provider could also choose to dispense fewer pills during the shortage (e.g. dispensing for one month to patients instead of two), requiring patients to return more frequently; or they could refer/transfer patients to other clinics where drugs are available or turn patients away without drugs until the shortage ends.

At the level of the patient, a stock shortage or stock-out could result in behaviour changes that would affect adherence to care and treatment for both ART-experienced and ART-naïve patients. A previous study reported that stock shortages played a major role in patients' adherence to ART because clinic staff had to dispense fewer pills to patients, often borrowed from nearby clinics, or sent patients away with no drugs and asked them return later [11]. Changes in care and treatment requiring patients to return to the clinic more frequently or travel longer distances to receive necessary drugs increase the economic burden of transport costs and the possibility of lost wages for patients, both of which are well-known barriers of adherence to HIV care and treatment [12–14]. A change in behaviour resulting in poor adherence to care and treatment could increase a patients' risk of viral load failure, loss to follow-up and ultimately death [12–14].

The length of the stock shortage or stock-out would be a strong determinant of the impact on HIV care and treatment. In South Africa, the tenofovir stock shortage was fairly short (roughly 7 months) and not all clinics were affected [2]. Nevertheless, it is important to document and quantify the effects of a stock shortage on treatment outcomes to show how clinics could alter patient care to help individuals remain in care and on treatment during a shortage and to assess patient behaviour and treatment outcomes in response to the modification in care and ARV availability. Using data from four public sector clinics in South Africa, two of which experienced a tenofovir stock shortage and two that did not, we investigated various mechanisms, at the level of the provider and the patient, to understand how the 2012 tenofovir stock shortage affected the HIV care and monitoring of patients accessing ART.

Methods

Cohort description

This study used data from the Right to Care Clinical HIV cohort. Right to Care is a non-profit organisation that supports HIV care and treatment services for roughly 5% of all HIV-positive patients in South Africa at geographically dispersed clinics. The clinics began initiating patients onto treatment in 2004 when large-scale roll-out of HIV treatment began in South Africa. The largest and most well-described site is the Themba Lethu Clinic, which has initiated over 27 000 patients on treatment since 2004 [15]. The Right to Care Clinical HIV cohort contains data on close to 130 000 patients across seven clinics, more than 90 000 of whom have initiated ART. Right to Care-supported clinics provide care in accordance with the national treatment guidelines [16, 17]. Each clinic collects patient-level data using an electronic record system (TherapyEdge-HIV™). All data, including demographic, clinical conditions, laboratory test results and medications (ARV and non-ARV related) are entered either by trained data capturers or in real time by clinicians.

Use of the Right to Care Clinical HIV cohort data was approved by the Human Research Ethics Committee of the University of the Witwatersrand. Approval for analysis of anonymised data was granted by the Institutional Review Board of Boston University.

Study design

We assessed the effect of the tenofovir stock shortage on various provider- and patient-level mechanisms to evaluate how the shortage affected the HIV care, monitoring and outcomes of patients accessing ART. Data were collected prospectively as part of routine care at four Right to Care-supported clinics in rural Mpumalanga [18] and Gauteng (Themba Lethu Clinic [17, 19] and two clinics in central (JHB) [19] and northern Johannesburg [20]). ART-naïve, HIV-infected patients >18 years of age who initiated first-line ART between 1 July 2011 and 31 March 2013 were included. The first-line ART of choice during the course of this study included the nucleoside reverse transcriptase inhibitor (NRTI) tenofovir (with stavudine or zidovudine, older NRTIs, available as alternatives) plus lamivudine (also an NRTI) and a choice of either efavirenz or nevirapine (non-nucleoside reverse transcriptase inhibitors (NNRTI)) [16, 17].

For outcomes, we evaluated changes in number of ART initiates, time between pharmacy visits, transfers, single-drug substitutions (defined as replacement of the NRTI only in first-line ART), treatment interruptions (defined as stopping the entire regimen for at least 2 weeks), missed pharmacy visits (defined as either not attending or being >7 days late for a scheduled pharmacy visit), loss to follow-up (>3 months late for last scheduled visit) and elevated viral load (defined as one viral load >1000 copies/ml [16, 17]).

Study variables

The dates of tenofovir shortage were determined via personal communication with Right to Care's head pharmacist [21] and confirmed in the clinical data. During the shortage, running from 1 February 2012 to 31 August 2012, two of the four clinics included in our analysis (Rural Mpumalanga clinic and Themba Lethu Clinic) experienced a shortage of tenofovir, the recommended NRTI for first-line ART, and were providing stavudine or zidovudine for patients initiating ART. As the shortage was not national (only 20% of clinics were affected [2]), the other two clinics in Johannesburg were used for comparison as they had a consistent supply of tenofovir.

The primary exposure of interest was the tenofovir stock shortage broken down into three time periods: before (1 July 2011–31 January 2012), during (1 February 2012–31 August 2012) or after (1 September 2012–31 March 2013) the shortage. At the time of the shortage, clinicians were to place all patients (both current patients and new initiates) on stavudine or zidovudine, unless they had contraindications to the drugs, instead of tenofovir and switch back to tenofovir once it became available [8].

Provider mechanisms

To assess whether clinics made adjustments to patient care to mitigate the impact of the stock shortage, we evaluated the following outcomes: (i) number of ART initiates to determine whether providers were restricting the number of new patients they were putting on to treatment; (ii) time between pharmacy visits to determine whether the number of pills dispensed decreased requiring patients to return to the clinic more frequently for drug pickups; (iii) transfers to determine whether patients were being formally transferred to other clinics that had not experienced shortages; (iv) treatment interruptions (defined as stopping the entire regimen for at least 2 weeks) to assess whether patients were discontinuing therapy; and (v) single-drug substitutions (defined as replacement of the NRTI only in first-line ART) to help determine whether providers were switching to different drugs as was recommended. For the outcome of single-drug substitutions, during the stock shortage the expectation was that patients that had been initiated or switch on to the older NRTIs would substitute with tenofovir when it became available. As such, we would expect patients on stavudine or zidovudine to experience higher rates of substitution either because they were taking more toxic drugs [22–30] or because clinicians were following the directive to switch patients to tenofovir once available.

To determine whether providers were placing patients with contraindications to tenofovir (such as females, patients with high body mass index or insufficient renal function [16, 17]) on the older NRTIs, we used log-binomial regression to evaluate potential demographic (i.e. age and sex) and clinical (i.e. creatinine clearance levels, CD4 count, haemoglobin levels, body mass index, WHO staging and tuberculosis) characteristics as predictors of not receiving tenofovir during the shortage. Creatinine clearance was categorised according to the U.S. National Kidney Foundation's Kidney Disease Outcome Quality Initiative (K/DOQI) as normal (>90 ml/min), mild (60–89 ml/min), moderate (30–59 ml/min) and severe (<30 ml/min) renal insufficiency [31].

Patient mechanisms

To assess whether patient behaviour or adherence to therapy changed during the shortage, we evaluated the following outcomes: (i) proportion of visits missed (defined as either not attending or being >7 days late for a

scheduled pharmacy visit) to determine whether the increased frequency of pharmacy visits resulted in reduced compliance with visit schedule; (ii) loss to follow-up (>3 months late for last scheduled visit) to determine whether any patients were more likely to leave care; and (iii) elevated viral load (defined as one viral

Table 1 Demographic and clinical characteristics of patients stratified by if they attended the clinic before, during or after the period of shortage at 4 HIV clinics in South Africa (n = 10 895)

Variable		Patients 1 July 2011 to 1 February 2012	Patients 2 February 2012 to 1 September 2012	Patient 1 September 2012 to 31 March 2013	All patients included
		Rural Mpumalanga clinic			
		n = 479	n = 345	n = 219	n = 1043
NRTI	Tenofovir, n (%)	443 (93.5)	127 (36.8)	196 (89.5)	766 (73.4)
NNRTI	Efavirenz, n (%)	467 (97.5)	328 (95.1)	211 (96.4)	1006 (96.5)
Gender	Female, n (%)	297 (62.0)	217 (62.9)	143 (65.3)	657 (63.0)
WHO Stage	III/IV, n (%)	104 (21.7)	70 (20.3)	54 (24.7)	228 (21.9)
Tuberculosis	Yes, n (%)	30 (6.3)	14 (4.1)	21 (9.6)	65 (6.2)
Age (years)	Median (IQR)	38.5 (32.0–47.2)	38.5 (31.7–46.1)	38.6 (31.9–46.2)	38.5 (31.9–46.6)
CD4 count (cells/μl)	Median (IQR)	178.5 (73.0–273.0)	277.3 (184.9–338.7)	239.0 (119.0–340.0)	215.5 (116.0–308.0)
Body mass index (kg/m^2)	Median (IQR)	21.3 (18.6–25.0)	21.5 (18.5–25.3)	22.7 (19.2–25.9)	21.8 (18.7–25.4)
Haemoglobin (μg/dl)	Median (IQR)	11.1 (9.4–12.2)	11.5 (9.7–12.9)	11.1 (9.1–12.7)	11.2 (9.5–12.6)
		Themba Lethu clinic			
		n = 1781	n = 1767	n = 928	n = 4476
NRTI	Tenofovir, n (%)	1605 (90.1)	1411 (79.9)	769 (82.9)	3785 (84.6)
NNRTI	Efavirenz, n (%)	1647 (92.5)	1679 (95.0)	881 (94.9)	4207 (94.0)
Gender	Female, n (%)	1049 (58.9)	1074 (60.8)	537 (57.9)	2660 (59.4)
WHO Stage	III/IV, n (%)	413 (23.2)	385 (21.8)	188 (20.3)	986 (22.0)
Tuberculosis	Yes, n (%)	146 (8.2)	115 (6.5)	52 (5.6)	313 (7.0)
Age (years)	Median (IQR)	37.8 (31.7–44.9)	37.9 (31.6–44.4)	37.7 (31.5–45.1)	37.8 (31.6–44.8)
CD4 count (cells/μl)	Median (IQR)	164.0 (73.0–249.0)	179.0 (72.0–281.0)	156.0 (57.0–277.0)	168.0 (70.0–268.0)
Body mass index (kg/m^2)	Median (IQR)	22.3 (19.5–26.1)	22.3 (19.8–26.2)	22.8 (19.5–26.2)	22.4 (10.7–26.2)
Haemoglobin (μg/dl)	Median (IQR)	11.9 (10.4–13.4)	12.2 (10.4–13.6)	12.4 (10.6–13.8)	12.1 (10.5–13.5)
		Northern JHB clinic			
		n = 859	n = 988	n = 778	n = 2625
NRTI	Tenofovir, n (%)	784 (91.3)	898 (90.9)	727 (93.4)	2409 (91.8)
NNRTI	Efavirenz, n (%)	769 (89.5)	866 (87.7)	726 (93.3)	2361 (90.0)
Gender	Female, n (%)	516 (60.1)	658 (66.6)	467 (60.0)	1641 (62.5)
WHO Stage	III/IV, n (%)	214 (24.9)	138 (14.0)	87 (11.2)	439 (16.7)
Tuberculosis	Yes, n (%)	71 (8.3)	47 (4.8)	23 (3.0)	141 (5.4)
Age (years)	Median (IQR)	36.4 (30.6–43.4)	36.7 (30.7–43.4)	35.4 (30.0–42.3)	36.2 (30.4–43.1)
CD4 count (cells/μl)	Median (IQR)	136.0 (67.0–196.0)	190.0 (103.0–263.0)	176.0 (81.0–268.0)	165.0 (82.0–248.0)
Body mass index (kg/m^2)	Median (IQR)	23.2 (20.3–26.9)	24.8 (21.6–29.2)	24.7 (22.0–28.7)	24.4 (21.4–28.4)
Haemoglobin (μg/dl)	Median (IQR)	11.8 (10.2–13.3)	12.1 (10.6–13.6)	11.9 (10.5–13.4)	11.9 (10.5–13.4)
		Central JHB Clinic			
		n = 998	n = 946	n = 807	n = 2751
NRTI	Tenofovir, n (%)	902 (90.4)	847 (89.5)	720 (89.2)	2469 (89.8)
NNRTI	Efavirenz, n (%)	937 (93.9)	895 (94.6)	772 (95.7)	2604 (94.7)
Gender	Female, n (%)	643 (64.4)	625 (66.1)	549 (68.0)	1817 (66.1)
WHO Stage	III/IV, n (%)	249 (25.0)	189 (20.0)	180 (22.3)	618 (22.5)
Tuberculosis	Yes, n (%)	116 (11.6)	97 (10.3)	103 (12.8)	316 (11.5)
Age (years)	Median (IQR)	35.6 (29.8–42.2)	35.2 (29.9–41.7)	34.4 (28.8–40.1)	35.1 (29.5–41.6)
CD4 count (cells/μl)	Median (IQR)	177.0 (90.0–280.0)	199.0 (97.0–286.0)	207.0 (108.0–326.0)	193.0 (96.0–294.0)
Body mass index (kg/m^2)	Median (IQR)	23.4 (20.9–27.0)	23.9 (21.0–27.9)	23.7 (20.7–27.7)	23.6 (20.9–27.6)
Haemoglobin (μg/dl)	Median (IQR)	11.8 (10.2–13.3)	11.9 (10.4–13.2)	11.7 (10.3–13.1)	11.7 (10.3–13.2)

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; WHO, World Health Organization.

load >1000 copies/ml [16, 17]) as an indicator of adherence to treatment. We also looked at the effect on mortality and CD4 response in our analysis and, as expected due to the length of follow-up, we found no effect of the stock shortage on these outcomes and did not report them here.

Statistical analysis

Patient demographic and clinical characteristics at ART initiation were summarised with descriptive statistics and stratified by the three time periods: before (1 July 2011–31 January 2012), during (1 February 2012–31 August 2012) or after (1 September 2012–31 March 2013) the stock shortage. For both provider- and patient-level outcomes, we used linear regression to fit splines with knots at the beginning (1 February 2012) and end (31 August 2012) of the tenofovir stock shortage and displayed results graphically by clinic to show trends over time. We fitted lines between the knots for the outcomes of number of ART initiates and days between pharmacy visits as they are absolute values aggregated by calendar month for each clinic, while we fitted curves for all other outcomes as they were binary and measured at the level of the individual.

As we have three time periods (before, during and after the shortage), we used difference-in-difference models to estimate risk differences (RD) and corresponding 95% confidence intervals (CI) to help determine the effect of exposure to the stock shortage on all outcomes. Each outcome was regressed on an indicator of time (before, during and after the stock shortage), an indicator for clinics exposed to the stock shortage (rural Mpumalanga clinic and Themba Lethu Clinic) or not exposed (central and northern Johannesburg clinics), demographic (i.e. age, sex and clinic) and clinical (i.e. CD4 count, haemoglobin levels, body mass index, WHO staging, tuberculosis and the NNRTI (nevirapine or efavirenz) used in first-line regimen) characteristics at ART initiation.

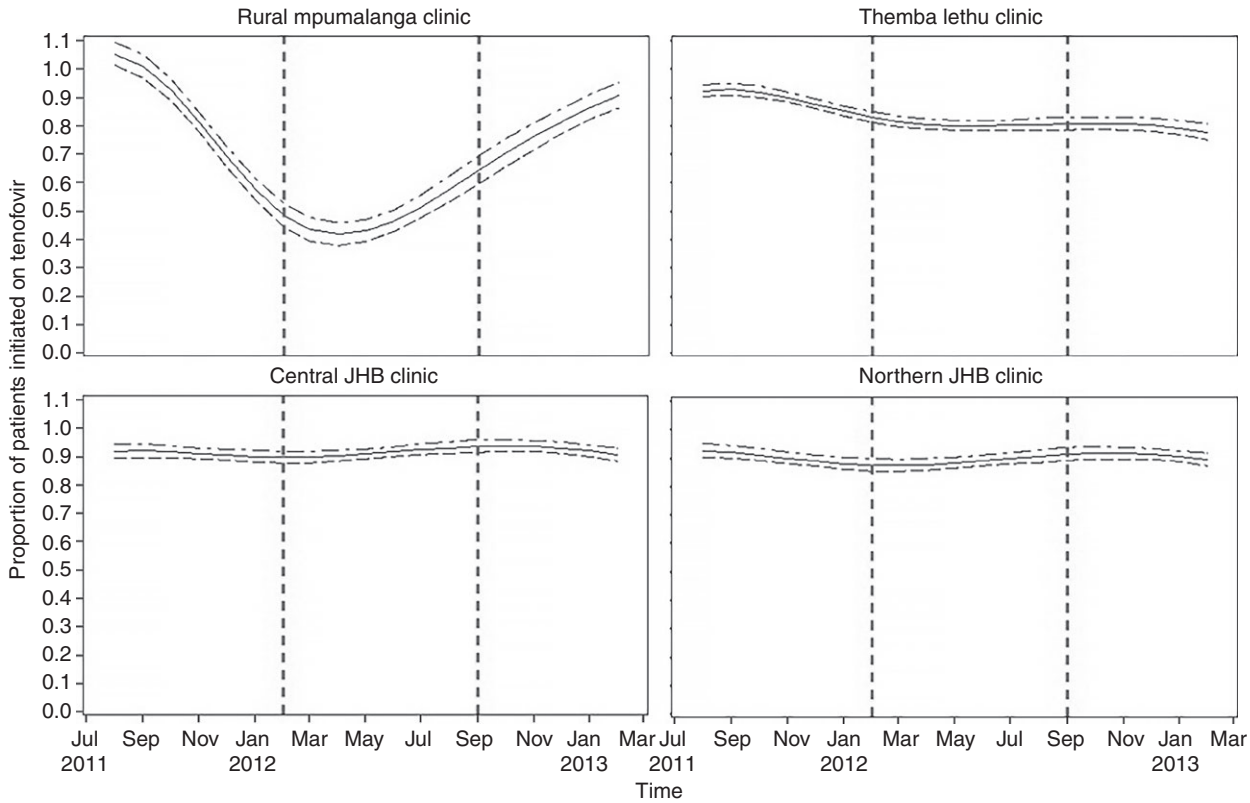

Figure 1 Trends in the proportion of HIV-positive patients initiating tenofovir at four government sector clinics in South Africa. *Red vertical bars represent the time period of the tenofovir stock shortage. **Transformation regression models run using PROC TRANSREG in SAS.

Results

In total, 10 895 treatment-naïve, non-pregnant, patients >18 years of age initiated a standard first-line ART regimen between 1 July 2011 and 31 March 2013. At ART initiation, patients had a median CD4 count of 177 cells/mm^3 (IQR: 83–273 cells/mm^3), were predominately female (60.6%) and had a median age of 36.8 years (interquartile range (IQR): 30.7–43.8 years). When stratified into the three time periods and by clinic, patients attending clinics before, during or after the shortage were similar on demographic and clinical characteristics within clinics (Table 1).

Tenofovir stock shortage

Table 1 and Figure 1, which shows the trend in the proportion of initiating tenofovir over the follow-up period for each clinic, show that during the stock shortage, upwards of 70% of patients initiating ART at the rural Mpumalanga clinic and 20% of patients at Themba Lethu Clinic were being initiated on a stavudine- or zidovudine-based regimen, instead of tenofovir, substantially higher than before or after the shortage. Over the entire time period of study, the control clinics (central and northern Johannesburg) showed no temporal trend in tenofovir use.

Provider mechanisms

We also assessed whether clinics modified patient care and treatment during the stock shortage to mitigate its impact on outcomes. We found a slight decline in the number of patients initiating ART during the period of the tenofovir shortage (Figure S1), with the greatest decline in the number of new initiates at Themba Lethu Clinic. However, the decline at Themba Lethu began prior to the stock shortage and continued in the period after, suggesting it may have had little to do with the shortage itself, and most likely due to the shift to nurse-

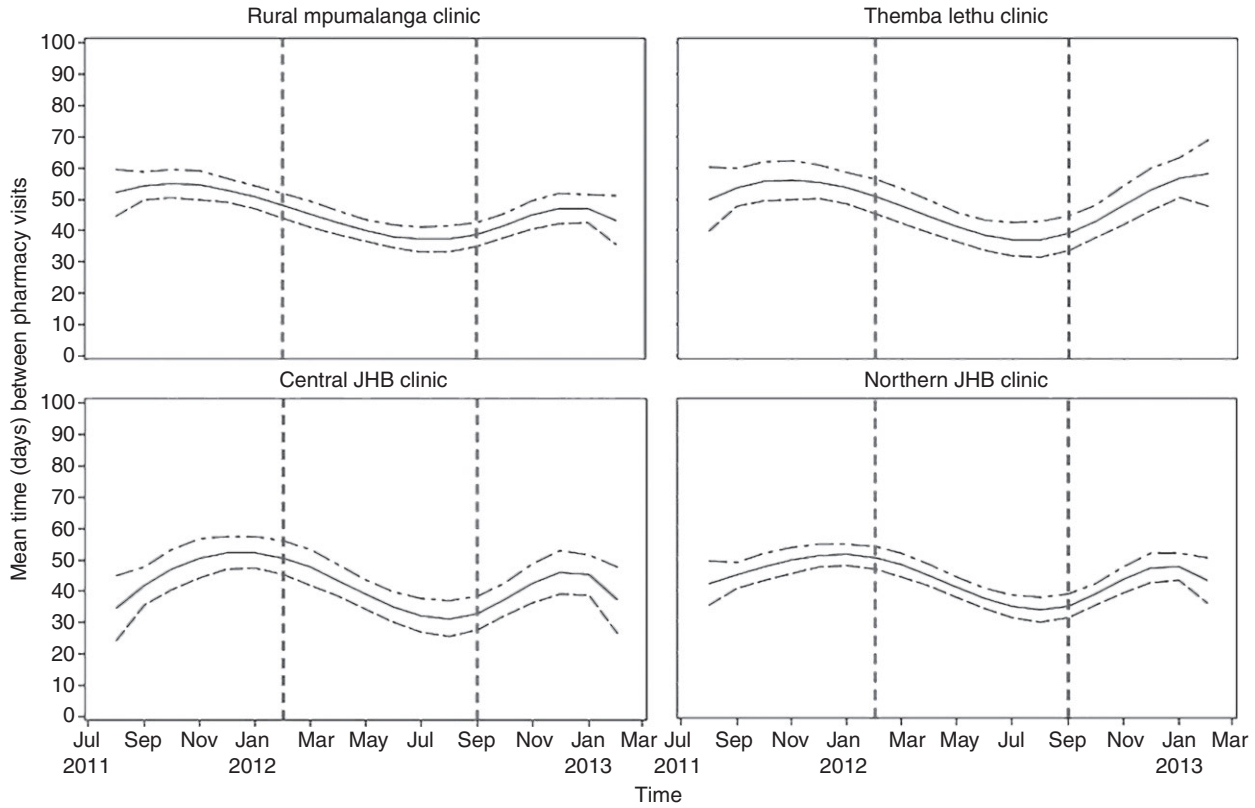

Figure 2 Trends in the average number of days between pharmacy visits in four government sector clinics in South Africa. *Red vertical bars represent the time period of the tenofovir stock shortage. **Transformation regression models run using PROC TRANSREG in SAS.

initiated and managed HIV care [31, 32]. We saw a decrease in average days between pharmacy visits during the shortage (Figure 2). Prior to the shortage, there were roughly 50 days between visits, which decreased to about 35 days during the shortage and increased back to 50 days after the shortage was resolved. In addition, we found no significant difference in the trends in the proportion of patients needing a single-drug substitution at all four clinics (Figure 3) and little evidence that the shortage affected transfers (Figure S2) to other facilities or treatment interruptions (Figure S3) as trends either remained roughly constant over the period of follow-up or difference-in-difference models (Table S1) showed no statistical significance difference between the time periods. Difference-in-difference models also showed little impact on our other outcomes during the period of the stock shortage compared with before when accounting for overall trends (Table S1). We did, however, see a small but significant decrease in the risk of single-drug substitutions after (RD: −1.6; 95% CI: −2.7, −0.5%) the shortage compared with before (Table S1).

When evaluating whether or not clinics were prioritising certain patients for tenofovir during the stock shortage, we found that patients with mild (60–89 ml/min) (risk ratio (RR): 1.75; 95% CI: 1.40, 2.18) to moderate/severe (<60 ml/min) (RR: 5.39; 95% CI: 4.28, 6.80) renal insufficiency (measured by creatinine clearance levels) were at increased risk of not receiving tenofovir during the shortage compared with those that had normal creatinine clearance levels (>90 ml/min) (Table S2). We also found that males (*vs.* females) and those with low haemoglobin levels (<10 μg/dl *vs.* >10 μg/dl) were at increased risk of not receiving tenofovir during the shortage.

Patient mechanisms

We evaluated whether patient behaviour and adherence to ART (as measured by a detectable viral load) changed during the stock shortage. We found no variation in loss to follow-up (Figure S4), while there is some suggestion that the trend in the proportion of patients experiencing

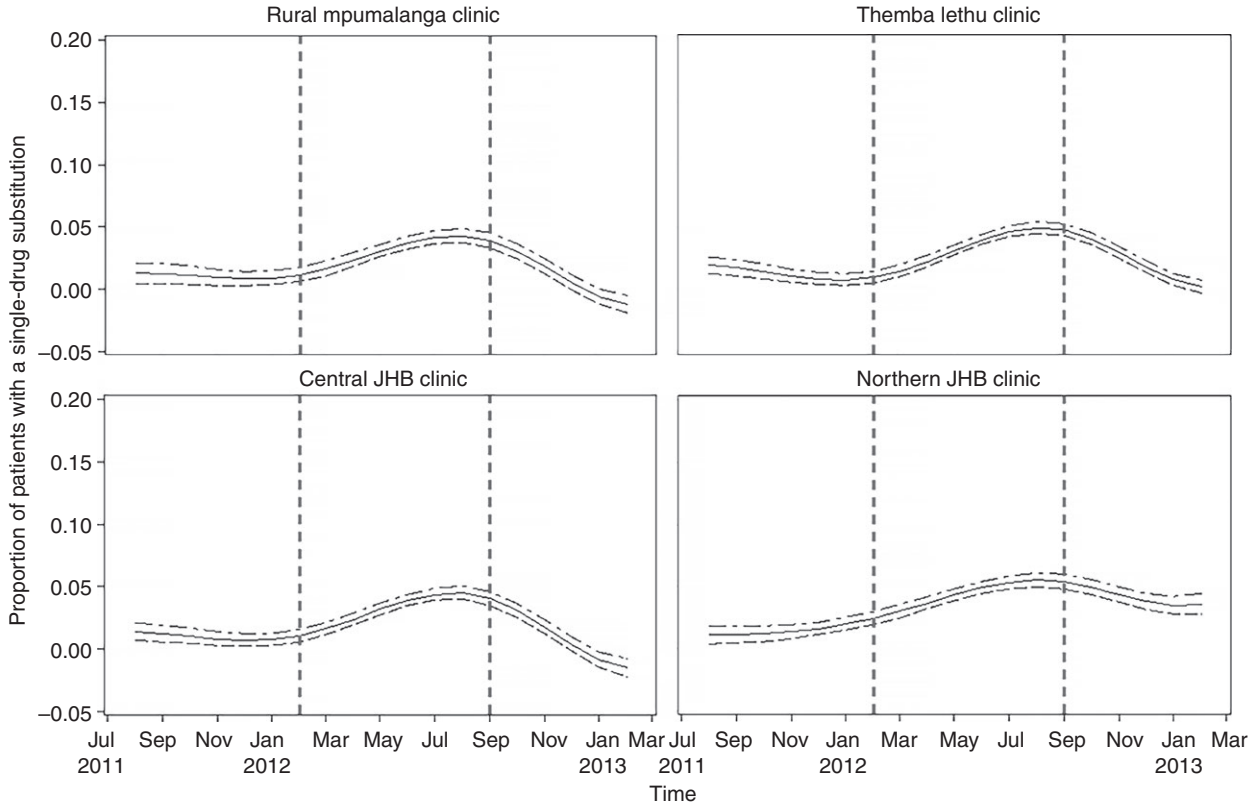

Figure 3 Trends in the proportion HIV-positive patients experiencing a single-drug substitution in four government sector Right to Care clinics, South Africa. *Red vertical bars represent the time period of the tenofovir stock shortage. **Transformation regression models run using PROC TRANSREG in SAS.

an elevated viral load increased after the shortage (Figure S5). However, the trend occurred in all four clinics, suggesting that it may not be due to the stock shortage. We also found an increase in the proportion of patients at the rural Mpumalanga clinic having a missed pharmacy visit during (~20%) the stock shortage period compared with before (~10%) (Figure 4). Difference-in-difference analysis confirmed an increase in missed pharmacy visits during (RD: 1.2%; 95% CI: 0.5, 2.0%) and after (RD: 2.4%; 95% CI: 1.6, 3.2%) the shortage (Table S1).

Discussion

Our study is the first to quantify the effects of a substantial tenofovir stock shortage in South Africa on provider and patient mechanisms and describe subsequent outcomes in HIV-positive adults at four large public sector HIV clinics. While imprecise, our results suggest a potential shift in how providers managed patients during the period of the shortage, mainly, a noticeable decrease in the average number of days between visits during the shortage compared with before or after at all four clinics. The decrease in number of days across all clinics could be cyclical due to the time of year and unrelated to the stock shortage, due to Right to Care-supported clinics receiving a smaller supply of drugs until the shortage was resolved or a clinic decision to dispense fewer pills at each drug pick-up visit until the shortage was resolved. We found that clinicians continued to follow national guidelines [16, 17] during the stock shortage as patients with poor renal function and those with low haemoglobin levels were less likely to receive tenofovir during the shortage. All other provider-level outcomes remained consistent across the study period.

With regard to behaviour change at the patient level as a result of the shift in provider management of patients, we found no evidence of an increase in loss to follow-up; however, there was an increase in the proportion of patients missing pharmacy visits. This was mainly driven by one site in rural Mpumalanga Province, where we saw roughly 10% of patients missing a visit prior to the stock shortage, a proportion which doubled during and after the stock shortage. Previous research has shown that the

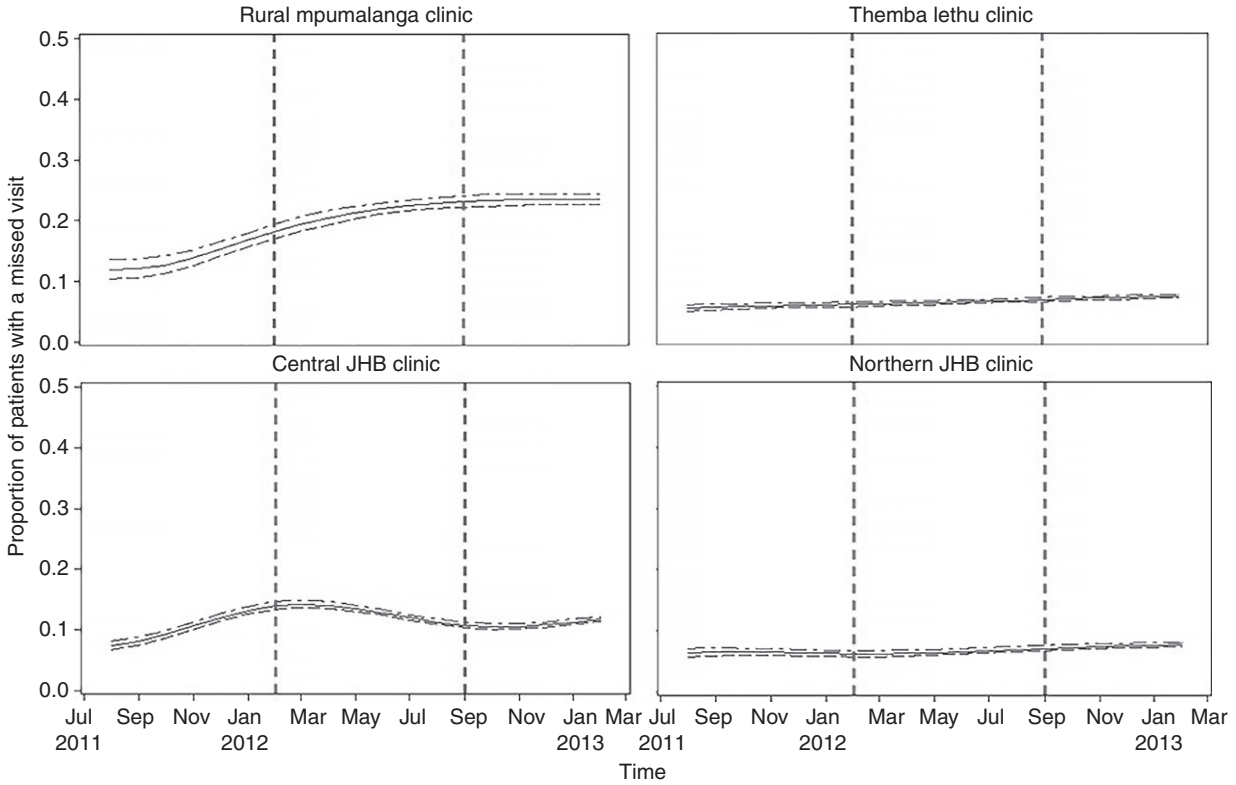

Figure 4 Trends in the proportion HIV-positive patients with missed visits in four government sector Right to Care clinics, South Africa. *Red vertical bars represent the time period of the tenofovir stock shortage. **Transformation regression models run using PROC TRANSREG in SAS.

type of community (urban *vs*. rural) can be a factor of adherence to HIV care and treatment, due to differences in community characteristics such as density of population, distance to and availability of clinics and hospitals and infrastructure within clinics [33, 34].

There is evidence, albeit limited, that HIV patients receiving ART exposed to ARV stock shortages or stock-outs (*vs*. those unexposed) in LMICs have an increased risk of viral load failure and attrition [3–6]. Our results, which show no impact of the shortage on loss to follow-up and viral load status, may be related to the fact that there was a stock shortage of tenofovir a not a complete stock-out. Clinics had access to stavudine and zidovudine during that period allowing them to continue to initiate new patients while maintaining treatment-experienced patients on tenofovir during the shortage. We also note that previous research has shown that death, loss to follow-up, immune response and viral load suppression are comparable for patients taking stavudine, zidovudine or tenofovir [9, 10, 22–30], suggesting that as long as care and monitoring of patients remain consistent, there should be little impact on these outcomes.

Access to one of the largest HIV clinic cohorts in South Africa that has been actively enrolling patients since the roll-out of treatment in the country in 2004 provided us an opportunity to evaluate the effect of the tenofovir shortage on provider- and patient-level outcomes in multiple public sector urban and rural clinics. However, our findings should be considered alongside potential limitations. First, this study represents patients from public sector clinics supported by an NGO partner and may, therefore, not be generalisable to other clinics or settings. Second, as data on pre-ART care are poorly captured in HIV care in LMICs, we were unable to show whether the shortage affected patients who had not yet initiated ART. Third, due to the short period of follow-up, we may have missed more subtle or longer-term effects that may be picked up later. Lastly, previous research reported conflict as a reason for ARV stock shortage or stock-out [5], which was not the case at Right to Care-supported sites, making our results less generalisable to conflict settings.

Conclusion

When health facilities lack the necessary drugs to treat HIV effectively, patients are at increased risk of developing and transmitting drug resistance strains, interrupting or defaulting on treatment, and ultimately increased risk of morbidity and mortality. While South Africa has made great strides to extend access to ART as well as increase the quality of the health services provided, patient care can be affected when stock shortages/outs occur. While our results show little effect on treatment outcomes when comparing patients accessing care during the shortage to those accessing care outside periods of shortage, this most likely reflects the clinics' ability to mitigate the crisis by continuing to keep patients' care and treatment as consistent as possible.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Trends in the absolute numbers of HIV-positive patients initiating ART at four government sector clinics in South Africa.

Figure S2. Trends in the proportion HIV-positive patients transferred out in four government sector Right to Care clinics, South Africa.

Figure S3. Trends in the proportion HIV-positive patients experiencing a treatment interruption in four government sector Right to Care clinics, South Africa.

Figure S4. Trends in the proportion HIV-positive patients lost to follow-up in four government sector Right to Care clinics, South Africa.

Figure S5. Trends in the proportion HIV-positive patients experiencing an elevated viral load in four government sector Right to Care clinics, South Africa.

Table S1. Difference-in-difference models assessing provider and patient level mechanisms on treatment outcomes during and after the stock shortage compared to before in the Right to Care Clinical HIV cohort, South Africa.

Table S2. Estimated risk ratios at ART initiation of not receiving tenofovir during the tenofovir shortage in Right to Care Clinical HIV cohort, South Africa.

Corresponding Author Alana T. Brennan, Department of Global Health, Boston University, Crosstown Center, 3rd Floor, 801 Massachusetts Ave, Boston, MA 02118, USA. Tel.: +1-617-414-1479; E-mail: abrennan@bu.edu