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Estimating the Effect of COVID-19 Pandemic Restrictions on Self-reported Antiretroviral Therapy Use and Late Refill Visits Among People Living With HIV in Rural South Africa

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Background: People living with HIV require reliable access to and adequate supply of antiretroviral therapy (ART) for viral suppression. The Deliver Health Study, a randomized trial conducted during the COVID-19 pandemic, found that home-delivered ART significantly increased viral suppression compared with clinic-based care. The effect of changing COVID-19 alert levels on self-reported ART use has not been quantified.

Setting: KwaZulu-Natal, South Africa.

Methods: Adults living with HIV were followed in the Deliver Health Study during October 2019–December 2020. We used difference-in-differences (DiD) to estimate the effect of changing COVID-19 alert levels during 3 distinct periods on self-reported missed ART doses (missed 0 vs. ≥1 doses in past week) for participants receiving home-delivered vs. clinic-based refills. We additionally estimated the effect of changing COVID-19 alert levels on late clinic ART refill visits (late vs. on-time). We used relative risk regression for both binary outcomes.

Results: Of 155 participants, 46% were women and the median age was 36 years. The mean number of missed weekly doses was 0.11, 0, and 0.12 in the home-delivery group and 0.09, 0.08, and 0.18 in the clinic group during periods 1, 2, and 3, respectively. There were no differences in relative risk of self-reported daily ART use between refill groups when comparing across periods [$DiD_{period\ 2\ vs.\ 1} = 1.05$; 95% confidence interval: 0.97, 1.13 and $DiD_{period\ 3\ vs.\ 2} = 0.99$; 95% confidence interval (CI): 0.91, 1.08]. In the clinic group, the risk of late refill visits was significantly higher during COVID-19 restrictions (vs. before alert level 5 implementation) and even after the COVID-19 alert level was downgraded to level 1 ($RR_{period\ 2\ vs.\ 1} = 1.83$, 95% CI: 1.34, 2.51 and $RR_{period\ 3\ vs.\ 2} = 1.71$; 95% CI: 1.43, 2.04).

Conclusion: The COVID-19 pandemic did not differentially impact self-reported ART adherence by the method of ART refills, but the risk of late clinic refill visits was significantly higher during COVID-19 restrictions and sustained after restrictions were loosened.

Key Words: HIV/AIDS, sub-Saharan Africa, HIV treatment, ART

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INTRODUCTION

While efforts to increase HIV status awareness through testing have been largely successful with 86% of people living with HIV globally knowing their HIV status at the end of 2022, the proportion of people living with HIV who were accessing treatment and who were virally suppressed was 76% and 71%, respectively.[1] In South Africa alone, nearly 8 million people are living with HIV, 74% of whom are on antiretroviral therapy (ART) and 65%[2] are virally suppressed. KwaZulu-Natal has the highest estimated HIV prevalence in South Africa at 27%.[3] Once diagnosed with HIV, all people living with HIV require a reliable ART supply for their lifetime or until a cure is available. Research in HIV care has centered around strengthening the HIV continuum, from HIV diagnosis, to ART initiation, and viral suppression for life.[4]

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A.S.T. and R.V.B. conceptualized the study. A.S.T., R.V.B., K.K.M., and A.A.S. developed the methods for the study. T.T.S. managed the study data. A.S.T. conducted statistical analyses and drafted the manuscript. All authors provided methodological and contextual input, reviewed, and approved the published version of the manuscript.

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Given the high HIV prevalence and importance of sustained HIV care, national scale-up of differentiated service delivery (DSD) models for HIV treatment tailored to specific patient populations are being expanded. The current standard-of-care in South Africa to refill ART prescriptions is for individuals to go in-person to clinics, with duration of ART refills often limited to 1 to 3 months.[5] One DSD model in South Africa focused on the delivery of medications, including ART, outside the clinic is the Centralised Chronic Medicines Dispensing and Distribution (CCMDD) program.[6] Resupplying ART through community-based venues has effectively increased ART coverage and adherence compared with clinic-based care[7] while decongesting clinics for attention to acute patients. Currently, CCMDD delivery services to community-based venues exist predominantly in urban areas, thus a DSD approach such as home-delivery of ART could cover the gap of CCMDD's services in rural settings.

During the COVID-19 pandemic, cancellation of health services due to government-imposed COVID-19 lockdowns were a major source of stress and anxiety for individuals with chronic conditions requiring consistent and frequent access to clinics.[8] As a response to country-wide COVID-19 lockdowns and associated service disruptions, home delivery of medication was rapidly implemented for individuals with chronic conditions in South Africa.[9] Multimonth scripts for people living with HIV also enabled sustained ART provision[10,11] in South Africa during the pandemic, with 1 study[12] demonstrating the success of 12-month ART scripts in KwaZulu-Natal for clinically stable people living with HIV. Beyond during large-scale disruptions in health services, novel strategies for refilling ART (eg, home-delivery) for people living with HIV can enable providers to continue to meet the needs of their patients without the patient barriers of physical commuting demands, long clinic wait times, and opportunity cost of missing work to refill prescriptions.

The Deliver Health Study found that home-delivered ART significantly increased viral suppression compared with clinic-based ART refills, including during COVID-19 lockdowns in rural South Africa (88% vs. 74%).[13] At each follow-up visit, Deliver Health Study participants were asked to self-report their number of missed ART doses. While viral suppression is the gold standard indicating treatment success for individuals living with HIV and is a composite measure of success for ART programs, frequent viral load measurements are not always feasible and alternative medication adherence measures are being researched. A recent study of a South African adolescent cohort found self-reported missed doses in the past week to be predictive of elevated viral load at 87% sensitivity and 19% specificity.[14] Ideally, self-reported daily ART use would provide a robust measure of ART delivery system resilience during times of social upheaval and during regular programming, allowing assessment of access to care. Interrupted time series analyses of the COVID-19 lockdown impact on HIV care in KwaZulu-Natal showed no marked changes in the number of ART refill visits[10] or HIV-related care clinic visits[15] immediately after lockdown (COVID-19 alert level 5) vs. before the lockdown. Another study found limited evidence of the association between health care access and ART adherence during the lockdown.[16] However, the impact of the COVID-19 pandemic itself and changes in COVID-19 alert levels on self-reported missed ART doses among adults living with HIV who received their ART refills through a DSD approach such as home-delivery vs. standard clinic care in rural South Africa is not known. Further, to our knowledge, the impact of COVID-19 restrictions on delayed ART refill visits at clinics in rural South Africa has not been characterized.

The primary aim of this study was to investigate the impact of the COVID-19 pandemic by estimating the effect of changing COVID-19 alert levels on self-reported daily ART use among people living with HIV receiving home-delivered vs. clinic-based ART refills in rural settings. We hypothesized that persons receiving home-delivered refills would report greater daily ART use than persons going to clinics to resupply due to uninterrupted access to refills through home delivery. For people living with HIV in the clinic-based care group only, we also estimated the effect of changing COVID-19 alert levels on the occurrence of late clinic refill visits as a secondary aim, hypothesizing a greater risk of late refill visits during more restrictive COVID-19 alert levels.

METHODS

Data Source

The Deliver Health Study (NIH R21MH115770; ClinicalTrials.gov ID: NCT04027153) was a pilot randomized controlled trial comparing fee for home delivery of ART with clinic-based ART refills in South Africa conducted from October 7, 2019, to December 31, 2020, during the COVID-19 pandemic. The objectives were to develop and test routing algorithms for mobile vans that deliver ART in rural, high prevalence HIV settings in South Africa and to evaluate the impact of a fee for home delivery of ART on viral suppression. A total of 162 individuals were enrolled in the Deliver Health Study. All participants were randomized to either receive their ART refills through home delivery through mobile vans or at clinics. Data on participant demographics, previous HIV testing history, clinical history, use of healthcare services, and barriers to care were collected. Plasma specimens were collected from participants at enrollment and at the exit visit for HIV-1 viral load testing. Participants completed a questionnaire on self-reported missed doses at each ART resupply visit. All participants were followed for at least 9 months with follow-up refill visits at months 1, 3, 6, and 9. While only 6 months of follow-up were originally planned, a month 9 visit was added to mitigate movement restrictions under the higher COVID-19 alert levels until an in-person exit visit could be conducted for the home-delivery group. The full study procedures have been previously published.[13] With its unique timing capturing the full first wave of the COVID-19 pandemic in South Africa, the Deliver Health Study was a suitable data source to answer the research question in this study.

Study Design

This study leveraged a natural experiment introduced by the COVID-19 pandemic. The South African government

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implemented 5-level alert system during the COVID-19 pandemic to ease into lockdown (see Supplemental Digital Content 1, http://links.lww.com/QAI/C274, summary of alert levels). Alert level 5 indicated high rates of COVID-19 infection with low health system readiness and had the most stringent lockdown measures, during which all nonessential and recreational travel were not permitted, schools and nonessential businesses were closed, public transportation was restricted, and individuals were required to stay at home unless to perform an essential service or seek emergency or chronic medical care.[17] The healthcare sector was considered an essential service with no restrictions placed on access to or delivery of healthcare services during lockdown,[15] although this does not account for reduced clinic capacity due to COVID-19-associated measures. Alert level 1 indicated low rates of COVID-19 infection with high health system readiness, during which most normal activities were resumed. Supplemental Digital Content 2, http://links.lww.com/QAI/C275, is a visual timeline of alert level changes during the first COVID-19 wave in South Africa.

The exposures for the primary and secondary aims of the study were (1) the implementation of the COVID-19 alert level 5 (lockdown) on March 27, 2020, and (2) downgrading the COVID-19 alert level to level 1 on September 21, 2020. There were 3 time periods of interest within the observed time frame of the Deliver Health Study: *before* the first COVID-19 alert, level 5 (lockdown) was implemented in South Africa from October 15, 2019, to March 26, 2020 (period 1), *during* the first COVID-19 lockdown (alert levels 5, 4, 3, and 2) in South Africa from March 27 to September 20, 2020 (period 2), and *after* the COVID-19 alert level was downgraded to level 1 in South Africa from September 21 to December 31, 2020 (period 3). Periods 1 and 2 were the relevant time periods to quantify the effect of implementing alert level 5, and periods 2 and 3 were the relevant time periods to quantify of the effect of downgrading to alert level 1. Participants in the Deliver Health Study were enrolled between October 15, 2019, and January 30, 2020. Thus, participants had varying follow-up windows and total follow-up time varied from participant to participant. Some participants had visits only during period 1 and period 2, some participants had visits only during period 2 and period 3, and some participants had visits during periods 1, 2, and 3.

Study Population and Eligibility Criteria

To be enrolled in the Deliver Health Study, individuals needed to meet the following criteria: age18 years and older, test positive for HIV during study screening, reside in the study community for the duration of follow-up, be eligible for ART by national guidelines or currently taking ART, willing to pay for home-delivery service, and able and willing to provide informed consent for study procedures. In addition to the inclusion criteria of the Deliver Health Study, for our analysis, individuals needed to have completed the study (ie, not lost to follow-up) and have a follow-up visit during at least 1 of the 3 time periods of interest.

Definition of Outcomes

The primary outcome measure was the number of ART doses missed in the past week (7 days), self-reported by participants at each follow-up visit. We operationalized the outcome as a binary variable, comparing zero reported missed ART doses (100% adherence) with ≥1 missed ART doses in the past week. We ran a sensitivity analysis with 1 missed dose as the cutoff (ie, 85% adherence) vs. ≥2 missed doses in the past week based on data from the literature on optimal adherence levels.[18] While HIV viral load is considered the gold standard for determining viral suppression, viral load measurements were only taken at study exit though participants were asked to self-report their number of missed doses at each follow-up visit. As a comparison, we examined if there was a difference in self-reported daily ART use and HIV viral suppression (undetectable HIV viral load), defined as having less than 20 copies per milliliter of blood, based on HIV plasma viral loads measured at study exit. We conducted a complete case analysis per time period, including individuals who had available data in the analytic data set of each time period. For example, if an individual had outcome data available in periods 1 and 2 but not 3, they were still included as part of the analytic data set in periods 1 and 2 but not for period 3. While it is not entirely plausible to assume that participants were missing self-reported data on missed ART doses completely at random, complete case analysis was a reasonable approach as there were only 8 of 611 observations (1%) with missing data on the number of ART doses missed in the past week, which would not have changed our results significantly if a single or multiple imputation approach was used to recover those 8 observations.

For the clinic-based care group only, we had a secondary outcome measure of late vs. on-time ART refill visits to assess if participants in the clinic-based care group were able to refill their ART before their prior prescription ran out. The goal of including this secondary outcome was to help quantify the impact of changing COVID-19 alert levels in South Africa on delayed clinic visits among people living with HIV in rural areas.

Statistical Analysis

To estimate the effect of changing COVID-19 alert levels on ART adherence of people living with HIV receiving home-delivered vs. clinic-based refills, we conducted 2 controlled differences-in-differences (DiD) analyses. First, to estimate the effect of COVID-19 alert level 5 being implemented, we compared the number of missed ART doses in the past week in the home-delivery group with the clinic-based ART refills group (the control) in period 1 vs. period 2. Second, to estimate the effect of downgrading to COVID-19 alert level 1, we compared the number of missed ART doses in the past week in the home-delivery group with the clinic-based ART refills group in period 2 vs. period 3. For the secondary aim, we compared the occurrence of late clinic ART refill visits in period 1 vs. period 2 and in period 2 vs. period 3.

For both primary and secondary aims, we used relative risk (RR) regression with sandwich estimators to obtain

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robust standard errors (generalized linear models with Poisson distribution and log link) because RRs were our quantity of interest and the prevalence of both zero missed ART doses and late ART refill visits were common in our study population (thus, odds ratios estimated from logistic regression would not have approximated the RRs[19]). We reported differences in RRs with corresponding 95% confidence intervals for the primary aim and RRs with 95% confidence intervals for the secondary aim. We shifted the time periods of interest forward by 7 days to account for the time lag of the outcome asking participants to recall on their number of missed doses in the past week. Thus, period 1 was considered October 15, 2019,–April 2, 2020; period 2 was April 3–September 30, 2020; and period 3 was October 1–December 31, 2020. We assumed the clinic-based care group was a good comparison group for the home-delivered refills group since it demonstrated what access to ART refills for people living with HIV would have been in South Africa in the absence of the home-delivery intervention. All analyses were conducted at the visit level. We used the Pearson χ^2 (2-sided) test at the $P < 0.05$ level to determine if there was a significant association between self-reported missed ART doses and viral suppression. More detailed statistical analysis methods and model equations are reported in Supplemental Digital Content 3, http://links.lww.com/QAI/C276.

RESULTS

After excluding 7 participants who were lost to follow-up, there were 155 participants in our study. Of those lost to follow-up, 6 participants were in the clinic-based care group, 43% were women, median age was 37 years, and all except 1 participant completed their month 6 follow-up visit but did not have an exit visit or viral load measurement. Of the 155 participants included in our study, 46% were women and the median age was 36 years (Table 1). The majority of participants (67%) knew their HIV status at baseline, of whom 95% were currently taking ART. One-third of participants did not know their HIV status before study screening and newly initiated ART. All study participants

TABLE 1. Characteristics of People Living With HIV From the Deliver Health Study by ART Refill Method, 2019–2020

	ART Refill Method		
	Home Delivery (N = 81)	Clinic-Based (N = 74)	Total (N = 155)
Characteristic	Median (IQR) or n (%)		
Age at baseline (yr)	38.00 (10.00)	34.00 (10.00)	36.00 (12.00)
Gender			
Women	36 (44.4)	35 (47.3)	71 (45.8)
Men	45 (55.6)	39 (52.7)	84 (54.2)
Marital status at baseline			
Divorced or widowed	5 (6.2)	4 (5.4)	9 (5.8)
Member of an unmarried couple	30 (37.0)	32 (43.2)	62 (40.0)
Single	40 (49.4)	38 (51.4)	78 (50.3)
Married	6 (7.4)	0 (0)	6 (3.9)
Educational attainment at baseline			
Primary	16 (19.8)	24 (32.4)	40 (25.8)
Secondary	57 (70.4)	40 (54.1)	97 (62.6)
Tertiary and above	8 (9.9)	10 (13.5)	18 (11.6)
Employment status at baseline			
Employed	33 (40.7)	27 (36.5)	60 (38.7)
Unemployed	48 (59.3)	47 (63.5)	95 (61.3)
Knowledge of HIV status at baseline			
Yes, I knew my status	53 (65.4)	51 (68.9)	104 (67.1)
No, I found out today	28 (34.6)	23 (31.1)	51 (32.9)
ART use at baseline (among those who knew their HIV status, n = 104)			
Yes, currently on ART	51 (96.2)	48 (94.1)	99 (95.2)
I have taken in the past but I have stopped taking them	1 (1.9)	2 (3.9)	3 (2.9)
Never taken ART	1 (1.9)	1 (2.0)	2 (1.9)
WHO clinical HIV status at baseline			
Stage 1	78 (96.3)	71 (95.9)	149 (96.1)
Stage 2	3 (3.7)	3 (4.1)	6 (3.9)
Stage 3	0 (0)	0 (0)	0 (0)
Stage 4	0 (0)	0 (0)	0 (0)
Taking other medications besides ART or TPT	5 (6.2)	3 (4.1)	8 (5.2)
Virally suppressed at study exit (<20 copies per mL)	71 (87.7)	55 (74.3)	126 (81.3)

HIV, human immunodeficiency virus; IQR, interquartile range; TPT, tuberculosis preventive treatment; WHO, World Health Organization.

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were taking the tenofovir/emtricitabine/efavirenz (TDF/FTC/EFV) ART regimen. Eighty-one participants received ART refills through home delivery compared with 74 participants who received standard clinic-based care. Most participants (n = 120; 82%) reported taking 100% of daily ART doses in the past week for the entire duration of the study. Twenty-two participants (14%) reported 75% adherence across the study period, 1 participant (1%) reported 67% adherence, and 5 participants (3%) reported ≤50% adherence. Of those receiving home-delivered refills, 80% (65/81) reported taking 100% of daily ART doses in the past week compared with 84% (62/74) of those receiving clinic-based refills.

The 155 participants accrued a total of 603 ART refill visits over the study period, after excluding 8 visits missing data on the number of ART doses missed in the past week. The total number of ART refill visits included in the period 1, period 2, and period 3 data sets were 291 visits (across 150 participants), 180 visits (across 139 participants), and 132 visits (across 132 participants), respectively. For persons receiving home-delivered refills, the mean number of missed weekly doses was 0.11, 0, and 0.12 during periods 1, 2, and 3, respectively; with clinic-based refills, the mean number of missed doses was 0.09, 0.08, and 0.18 during periods 1, 2, and 3, respectively (Table 2). In the clinic group, the mean number of late refill visits over the study period was 2.32 (range: 1–3). Self-reported missed doses was not associated with viral suppression at exit at the 100% adherence level (Pearson $\chi^2 = 0.14$; P-value = 0.71) or at the ≥85% level (Pearson $\chi^2 = 0.03$; P-value = 0.85).

Difference-In-Differences of Missing ART Doses Between Home-Delivered vs. Clinic Refills

The RR of missing ART doses in a given week among participants receiving home-delivered ART refills was 1.05 times the RR among participants refilling ART at clinics in period 2 vs. period 1 but was not statistically significant [95% confidence interval (CI): 0.97, 1.13] (Table 3). Comparing period 3 with period 2, the RR of missing ART doses in a given week among participants receiving home-delivered ART refills was 0.99 times the RR among participants refilling ART at clinics, although was also not statistically significant (95% CI: 0.91, 1.08). When lowering the adherence cutoff from 100% to ≥85%, the results for both time period comparisons were unchanged ($DiD_{\text{period 2 vs. 1}} = 1.01$; 95% CI: 0.98, 1.06 and $DiD_{\text{period 3 vs. 2}} = 0.98$, 95% CI: 0.90, 1.06).

RR of Late Clinic Refill Visits Between Different Periods

Among participants refilling their ART at clinics, the risk of late ART refill visits during period 2 was 1.83 times (95% CI: 1.34, 2.51) the risk of late ART refill visits during period 1 (Table 4). The risk of late ART refill visits during period 3 was 1.71 times (95% CI: 1.43, 2.04) the risk of late ART refill visits during period 2.

Additional results are reported in Supplemental Digital Content 3, http://links.lww.com/QAI/C276.

DISCUSSION

In our study, we were able to quantify the effect of changing COVID-19 alert levels throughout the first COVID-19 wave in South Africa on self-reported ART daily dosing among people living with HIV receiving home-delivered or clinic-based refills by segmenting the study period to correspond to the dates of COVID-19 alert level changes. We were also able to assess the impact of changing COVID-19 alert levels on occurrence of late refill visits for those refilling ART at clinics only. While we did not observe

TABLE 2. ART Adherence* Self-Reported by People Living With HIV at Each ART Refill Visit During Different Time Periods of Varying COVID-19 Alert Levels Throughout the First COVID-19 Wave in South Africa, 2019–2020 (N = 603 Refill Visits)

	Period 1: Before Implementation of COVID-19 Alert Level 5†			Period 2: During COVID-19 Alert Levels 5, 4, 3, and 2‡			Period 3: After Downgrading to COVID-19 Alert Level 1§		
	October 15, 2019–March 26, 2020			March 27–September 20, 2020			September 21–December 31, 2020		
ART Refill Method	Mean Number of Missed Doses in Past 7 Days‖	Refill Visits With ≥1 Doses Missed in Past 7 Days Reported n (%)	Refill Visits With ≥2 Doses Missed in Past 7 Days Reported n (%)	Mean Number of Missed Doses in Past 7 Days‖	Refill Visits With ≥1 Doses Missed in Past 7 Days Reported n (%)	Refill Visits With ≥2 Doses Missed in Past 7 Days Reported n (%)	Mean Number of Missed Doses in Past 7 Days‖	Refill Visits With ≥1 Doses Missed in Past 7 Days Reported n (%)	Refill Visits With ≥2 Doses Missed in Past 7 Days Reported n (%)
Home delivery	0.11	16 (9.5)	10 (5.9)	0	0 (0)	0 (0)	0.12	3 (5.2)	4 (6.9)
Clinic	0.09	9 (7.4)	8 (6.6)	0.08	1 (1.1)	0 (0)	0.18	4 (5.4)	7 (9.5)

*The number of missed ART doses in the past 7 days was self-reported by participants at each study follow-up visit (months 1, 3, 6, and 9).

†Alert level 5 was equivalent to a full lockdown during which all nonessential activities and services were restricted. The total number of ART refill visits included in period 1 was 291 across 150 participants. There were 169 visits accrued by 81 participants in the home-delivery group and 122 visits accrued by 69 participants in the clinic group during period 1.

‡The total number of ART refill visits included in period 2 was 180 across 139 participants. There were 89 visits accrued by 65 participants in the home-delivery group and 91 visits accrued by 74 participants in the clinic group during period 2.

§The total number of ART refill visits included in period 3 was 132 across 132 participants. There were 58 visits accrued by 58 participants in the home-delivery group and 74 visits accrued by 74 participants in the clinic group during period 3.

‖The ART regimen was 1 daily dose. The possible range of missed doses in the past 7 days was 0–7.

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TABLE 3. Difference-In-Difference Estimates of Optimal Medication Adherence (100% and ≥ 85%) Comparing People Living With HIV Receiving Home-Delivered vs. Clinic-Based ART Refills Between Time Periods During the First COVID-19 Wave in KwaZulu-Natal, South Africa

Time Period Comparison	Optimal ART Adherence (in the Past 7 Days)	Difference in Relative Risk Ratio	95% Confidence Interval*
Period 2† vs. period 1‡	100% adherence: 0 missed doses vs. ≥ 1 missed doses	1.05	0.97, 1.13
	≥85% adherence: ≤ 1 missed doses vs. ≥ 2 missed doses	1.01	0.98, 1.06
Period 3§ vs. period 2†	100% adherence: 0 missed doses vs. ≥ 1 missed doses	0.99	0.91, 1.08
	≥ 85% adherence: ≤ 1 missed doses vs. ≥ 2 missed doses	0.98	0.90, 1.06

*Robust standard errors were estimated using the "sandwich" and "lmtest" packages in R.

†Period 2 = During COVID-19 alert levels 5, 4, 3, and 2. The total number of ART refill visits included in period 2 was 180 across 139 participants. There were 89 visits accrued by 65 participants in the home-delivery group and 91 visits accrued by 74 participants in the clinic group during period 2.

‡Period 1 = Before implementation of COVID-19 alert level 5 (lockdown). The total number of ART refill visits included in period 1 was 291 across 150 participants. There were 169 visits accrued by 81 participants in the home-delivery group and 122 visits accrued by 69 participants in the clinic group during period 1.

§Period 3 = After downgrading to COVID-19 alert level 1. The total number of ART refill visits included in period 3 was 132 across 132 participants. There were 58 visits accrued by 58 participants in the home-delivery group and 74 visits accrued by 74 participants in the clinic group during period 3.

significant differences in the RR of missing ART doses for people living with HIV receiving home-delivered vs. clinic-based ART refills between the different periods of changing COVID-19 alert levels as hypothesized, we did find that self-reported ART adherence was high during all 3 periods regardless of the ART refill method. Furthermore, participants in the clinic-based care group had a significantly greater risk of late ART refill visits in both time period comparisons.

While the home-delivery group of the Deliver Health Study was not affected by the COVID-19 pandemic lockdown in terms of access to ART refills, participants in the clinic-based refills group did experience disruptions to their care such as delayed clinic visits due to limited healthcare capacity or inability to commute to clinics because of reduced public transportation services during COVID-19 restrictions. However, we did not find significant differences in self-reported daily ART dosing between people living with HIV receiving ART refills from home-delivery vs. at clinics during or between each period in our study, suggesting limited evidence of the association between method of ART access and ART adherence during COVID-19, consistent with the literature on health services access and ART adherence.[16] A potential explanation for our finding is that the study staff in the Deliver Health Study made phone calls to each participant to monitor their ART initiation and care, regardless of which study arm they were randomized to. Thus, since all participants received ART monitoring, it is a reasonable finding that there were no differences in self-reported daily dosing between people living with HIV receiving home-delivered or clinic-based ART refills. Among those enrolled in a randomized cluster trial in Cape Town testing different community health worker interventions to improve ART adherence that was interrupted by COVID-19, 70% of participants stated they missed their community health worker's support in their HIV care during COVID-19 lockdowns.[16] The Deliver Health Study staff who made phone calls to participants for each follow-up visit could be viewed as a similar function as community health workers meeting with people living with HIV regularly to promote ART adherence and retention in care.

TABLE 4. Difference in Late ART Refill Visits Between Time Periods During the First COVID-19 Wave for People Living With HIV Refilling ART Supply at Clinics in KwaZulu-Natal, South Africa

Time Period Comparison	Relative Risk Ratio	95% Confidence Interval*
Period 2† vs. period 1‡	1.83	1.34, 2.51
Period 3§ vs. period 2†	1.71	1.43, 2.04

*Robust standard errors were estimated using the "sandwich" and "lmtest" packages in R.

†Period 2 = During COVID-19 alert levels 5, 4, 3, and 2. There were 91 visits accrued by 74 participants in the clinic group during period 2.

‡Period 1 = Before implementation of COVID-19 alert level 5 (lockdown). There were 122 visits accrued by 69 participants in the clinic group during period 1.

§Period 3 = After downgrading to COVID-19 alert level 1. There were 74 visits accrued by 74 participants in the clinic group during period 3.

An advantage of scaling up home-delivery of medication for people living with chronic conditions is that deliveries can be scheduled ahead of time, ensuring that clients receive their next medication refill before their existing refill running out. By contrast, needing to go in-person to refill one's ART supply requires taking personal time to commute to the clinic and waiting a long time to see a health care provider alongside patients with acute health conditions, among other potential barriers to care. The COVID-19 pandemic, particularly early on in 2020, created additional barriers to accessing care at clinics with movement and capacity restrictions implemented by the government and personal fears of COVID-19 infection before vaccines were available. This was reflected in our study findings as all participants in the clinic group had at least 1 late refill visit across the study period. To quantify the COVID-19 pandemic's impact on health care disruptions, we examined timeliness of ART refill visits for participants in the clinic arm only and found that participants refilling their ART at clinics had a significantly greater risk of late ART refill visits during period 2 (when varying levels of lockdown measures were in place) compared with before COVID-19 alert level 5 was implemented, which is consistent with what we would have expected due to lockdown restrictions on non-urgent care and reduced clinic capacities. There was also a significantly greater risk of late clinic refill visits after the COVID-19 alert level was downgraded to level 1 (period 3) compared with during period 2. A

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potential explanation for this observed trend is that individuals had greater competing interests (eg, return to work, errands) after lockdown restrictions were loosened, decreasing their availability to go to clinics for scheduled refill appointments compared with during period 2 with likely fewer competing interests. Another possible explanation is the development of concerns related to the COVID-19 pandemic that persisted even after the COVID-19 alert level was downgraded to level 1 in December 2020 and it was deemed "safe" to resume to regular activities. A study of telephone interviews with people living with HIV in KwaZulu-Natal during COVID-19 identified new concerns about picking up ART going forward, including COVID-19 infection risk, transportation availability, safety concerns, concern or knowledge that pick-up point is closed/no staff present, long queues, delay in being attending to, transportation cost, illness in self or family, and busy with work or family.[20]

In our study, self-reported daily ART dosing was high among people living with HIV before, during, and after COVID-19 lockdowns, regardless of ART refill method, but did not correlate with viral suppression. While not correlated with viral suppression in our study, medication adherence is a self-monitored task by patients which should be emphasized during HIV counseling services. In fact, a recent systematic review found that high levels of patient self-efficacy and physician-supported patient control over disease management (ie, a joint empowerment approach) promoted greater patient empowerment and medication adherence.[21] Even though there was a significant difference in the proportion of people living with HIV who were virally suppressed at exit in home-delivery vs. clinic-based care groups in the Deliver Health Study,[13] we did not observe a significant difference based on the self-reported measure of missed ART doses. While there was likely social desirability bias in the self-reported outcome measure, this reporting bias likely occurred in both groups of participants who received home-delivered and clinic-based refills (ie, non-differential misclassification) which would not have resulted in a biased effect estimate. With a retrospective study design, the measure of self-reported missed ART doses at each refill visit was the best variable that we could utilize as a proxy for adherence in our study. Future studies should consider using objective medication adherence measures in the design stage to minimize potential measurement bias, whether that is continued use of dried blood spots[22] or alternatives such as hair samples,[23] electronic adherence monitors,[24] and ingestible sensors.[25]

Limitations of this study included a small sample size resulting in limited statistical power, very specific time periods corresponding to changing COVID-19 alert levels during the first COVID-19 wave in South Africa resulting in limited generalizability, and self-reported ART adherence resulting in measurement error (internal validity) concerns. Strengths of our study included the use of data from a clinical trial which previously found that there was a significant increase in the proportion of people living with HIV who were virally suppressed for those receiving home-delivered vs. clinic-based ART refills, and the unique insights drawn about the impacts of changing COVID-19 alert levels on access to medication and HIV care for people living with HIV in rural settings.

Home delivery of ART allowed for uninterrupted access to refills during the COVID-19 pandemic when there were greater barriers to accessing in-person clinic-based care in rural South Africa. While home-delivered refills can reduce an individual's uncertainty about physically accessing ART resupply, we did not find a difference in the self-reported number of missed ART doses by method of ART refill (home-delivered vs. at-clinic) when comparing between or within time periods during the first COVID-19 wave in South Africa. All participants in the clinic-based refills group had at least 1 delayed refill visit during the first COVID-19 wave and were more likely to have a late clinic refill visit after the COVID-19 alert level 5 was implemented (vs. before COVID-19 lockdowns) and even after the COVID-19 alert level was downgraded to level 1 (vs. during COVID-19 alert levels 5, 4, 3, and 2). In rural South Africa, people living with HIV in standard clinic-based care experienced disruptions to ART refill access during the COVID-19 pandemic while home-delivery proved to be a reliable method of sustained ART provision. DSD approaches such as home-delivered ART is promising and could address current physical access or stigma barriers faced by people living with HIV and could potentially be bundled with the delivery of other medications with for people living with multiple chronic conditions.

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