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Research Paper

Estimating the effect of increasing dispensing intervals on retention in care for people with HIV in Haiti

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ABSTRACT

Background: Multi-month dispensing (MMD) for antiretroviral therapy (ART) is a promising care strategy to improve HIV treatment adherence. The effectiveness of MMD in routine settings has not yet been evaluated within a causal inference framework. We analyzed data from a robust clinical data system to evaluate MMD in Haiti.

Methods: We assessed 1-year retention in care among 21,880 ART-naïve HIV-positive persons who started ART on or after January 1, 2017, up until November 1, 2018. We used an instrumental variable analysis to estimate the causal impact of MMD. This approach was used to address potential selection into specific dispensing intervals because MMD is not randomly applied to individuals.

Findings: We found that extending ART dispensing intervals increased the probability of retention at 12 months after ART initiation, with up to a 24·2%-point increase (95%CI: 21·9, 26·5) in the likelihood of retention with extending dispenses by 30 days for those receiving one-month dispenses. We observed statistically significant gains to retention with MMD with up to an approximately 4-month supply of ART; +5·1%-points (95%CI: 2·4,7·8). Increasing dispensing lengths for those already receiving ≥5-month supply of ART had a potentially negative effect on retention.

Interpretation: MMD for ART is an effective service delivery strategy that improves care retention for new ART recipients. There is a potentially negative effect of increasing prescription lengths for those new ART recipients already receiving longer ART supplies, though more research is needed to characterize this effect given medication supplies of this length are not common for newer ART recipients.

1. Introduction

The last several decades have seen great strides in therapeutic regimens for HIV, leading to improved survival and quality of life for people with HIV [1,2]. However, achieving optimal health status at the population level requires both excellent therapeutic options as well as effective delivery models. These issues of care delivery are especially salient for vulnerable populations in limited-resource settings where managing an increasing number of people living with HIV and addressing high rates of attrition at all stages along the care continuum is particularly challenging [3]. Managing HIV care during crises such as global pandemics, such as Zika or COVID-19, adds even more challenges like safety concerns for patients and providers, as well as medication supply chain issues due to global transportation delays.

The differentiated care approach is a promising way to address the challenges of providing effective antiretroviral therapy (ART) for individuals with HIV [4,5]. One differentiated care strategy is to increase the number of days of ART supplied for stable individuals from the standard 1-month supply of ART. This strategy, called multi-month dispensing (MMD), has been promoted within The President's Emergency Plan For AIDS Relief (PEPFAR) programs since 2016 and shows great promise in improving retention in care and viral load suppression [3,6]. MMD is intended to increase treatment adherence by minimizing disruption to everyday life [5–7]. Additionally, in resource-limited healthcare systems that support an increasing number of people with HIV, strategies to improve health outcomes while also reducing the demands on care delivery systems are paramount. MMD decreases the interactions between HIV-positive patients and the healthcare delivery system and minimizes the human resources needed for the routine care of stable HIV-positive people. If longer dispensing intervals improve retention compared to the standard of care,

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Research in context

Evidence before this study

Global HIV service delivery targets can be challenging for low-resource countries, or areas with particularly vulnerable populations. Novel strategies are warranted to achieve these service delivery goals. There is minimal literature on the use of large, routine data sources used to examine the causal impact of person-centered policies such as multiple-month ART dispenses, and the subsequent implications for reaching ambitious global HIV care goals.

Added value of this study

This study provides a causal estimate of the effect of extending ART dispenses on retention in care in a low-resource setting and demonstrates that new individuals on treatment can be successful on care regimens with lower frequencies of return visits to healthcare facilities. Factors such as limited or high-cost transportation, coupled with long distances to healthcare facilities for many people living with HIV, make longer ART dispenses a valuable, person-centered care delivery strategy.

Implications of all the available evidence

In low-resource settings, such as Haiti, this research found that extending ART prescription lengths improves retention in care for most new ART recipients. This research refines existing ART guidelines in Haiti to specify a recommended ART prescription length of 3,4 months for new ART recipients.

or is at least non-inferior, MMD presents an opportunity to maintain care quality, while decreasing the resources needed to sustain HIV care programs. The COVID-19 pandemic makes it more imperative to investigate the effect of extending ART dispensing intervals on retention in care. Reducing interactions with the healthcare system helps minimize COVID-19 exposure for both clinical providers and medical care recipients.

The effectiveness of MMD within programmatic settings, and using routine data, has not been empirically evaluated within a causal inference framework [8]. Historically, HIV treatment guidelines and HIV care policies were derived from clinical trial data, often considered the gold standard for causal inference [9–11]. However, clinical trials are expensive, time intensive, and often of limited generalizability to vulnerable populations because these populations are difficult to recruit into research studies [10,12,13]. For resource-limited settings or for populations not represented in the clinical trial literature, observational data from routine clinical sources are valuable indicators of the care and health outcomes for people with HIV [14,15]. Current studies suggest an association between MMD and increased retention in care [16, 17], but operational research using programmatic data may help elucidate the causal impact on retention, supporting evidence from randomized trials. The question remains whether longer dispensing intervals lead to better retention due to increased convenience or whether the people selected for longer dispensing intervals are those mostly likely to be adherent. Existing studies of MMD effectiveness using routine data are limited by selection bias—people with HIV who are given longer prescription interval lengths are those who are believed to be stable and to have a high likelihood of adhering to the medication. We used a statistical approach designed to address inherent selection bias in ART dispensing intervals to estimate a causal effect of increasing dispensing intervals for new ART recipients on retention in care.

This study provides a novel and timely contribution to literature regarding the impact of this specific differentiated care strategy and how this strategy may be best applied to HIV-positive individuals in care in Haiti. Our findings can help estimate the effects of MMD in Haiti and elsewhere as part of HIV strategic planning or COVID-19 response. To our knowledge, our study is the first to use an existing, robust clinical data system to evaluate MMD at a national level. This study seeks to characterize the effect of MMD on retention in care for new ART recipients.

2. Methods

2.1. Data source

We retrospectively analyzed data from the iSanté HIV-specific electronic health record (EHR) from Haiti. iSanté supports data entry from forms used in the clinic as well as from interactive, point-of-care use [18,19]. iSanté is a networked system of longitudinal clinical encounter data used in more than 100 Haitian health facilities that offer HIV care and treatment [20]. iSanté includes information regarding demographics, laboratory history/results, diagnosis history, treatment history, and pharmacy records, as well as data fields for counseling and referrals recieved [18,21]. All records from health facilities with out-of-date data, defined as having less than 90% of visit forms saved to the iSanté consolidated server within 90 days of the person's visit [20], were excluded from our analysis for data quality control purposes.

2.2. Ethical review

The secondary use of de-identified individual-level data for this study received human subjects approval from University of Washington and the Haiti Ministry of Health's National Bioethics Committee. This project was also reviewed in accordance with the US Centers for Disease Control and Prevention (CDC) human research protection procedures and was determined to be research, but CDC investigators did not interact with human subjects or have access to identifiable data or specimens for research purposes,

2.3. Inclusion criteria

Our sample included ART-naïve HIV-positive individuals enrolled in iSanté who started ART on or after January 1, 2017, up until November 1, 2018, to assess 1-year retention (with a 30-day grace period) after their initial ART fill. People with HIV were included 1 year after MMD was introduced into the national HIV care guidelines in 2016 to account for delays in guideline implementation across facilities nationally. Individuals receiving any ART regimen (first-line, second-line, or third-line) were included in the analysis; people with HIV who never started ART were excluded.

2.4. Variables

Haitian ART guidelines during this time period recommended MMD after individuals were demonstrated to be stable on ART for 6 months [22,23] as the standard of care; stability is not well-defined in the guidelines and ultimately left to the judgment of the healthcare team. However, in practice, MMD was often allowed before the recommended 6-month time period as evidenced in the EHR data, with the range of dispensing intervals exceeding 1 month during the period immediately following ART initiation. The primary exposure was ART dispensing length in days, as obtained from pharmacy records. To assign exposure status, we calculated the average dispensing length over the first 6 months of treatment and applied that as the dispensing length of interest. Initial dispensing lengths may be significantly shorter than subsequent ones because clinicians may

test tolerability to specific ART drugs and monitor for evidence of toxicity [24]. We chose not to classify the exposure based on the refill interval that immediately precedes the 6-month point because attrition early in treatment can be high [20], and we wanted to estimate the effect of increasing dispensing interval on retention among a representative sample of new ART recipients. Additionally, there is high within-person variability in dispensing intervals during the first 6 months; therefore, selecting a single refill within this window could result in estimation that would possibly not be representative of an individual's early ART care history.

The outcome of interest for this study was a binary measure of retention in care (retained vs. not retained). Retention in care, or timely ART pickup, was defined as picking up an ART refill within 30 days of the scheduled ART pickup after 1 year in treatment (12-month follow-up). We used retention in care as a proxy for treatment adherence [25] and viral suppression [26]. Although iSanté does include information on laboratory values for HIV viral load, viral load results at the time of the study were inconsistently available in the EHR. Viral load test results from the 12-month follow-up visit were available in the electronic system for only approximately 40% of the sample. Although viral suppression is the gold standard for treatment success [26–28], this variable in the Haitian context was not included due to a high level of missing data (approximately 60% of the viral load data for the one-year follow-up visit in the sample had not been entered into the EHR at the time of data extraction).

Individual characteristics including sex, age, World Health Organization (WHO) clinical stage [29], body mass index (BMI) category, and provision of isoniazid for TB preventive treatment at ART initiation were included in all models, in addition to a categorical variable for facility ownership (public, private, and mixed) and facility network. The provision of isoniazid was included as a proxy indicator for provider adherence to treatment guidelines, because all people with HIV in Haiti who are new to ART and not receiving active TB treatment and report no symptoms of TB disease are recommended to receive TB preventative treatment [23]. The WHO stage and BMI category variables included a missing indicator if there was insufficient evidence in the medical record to determine these values, but complete information was available for the other key demographics and for exposure and outcome variables.

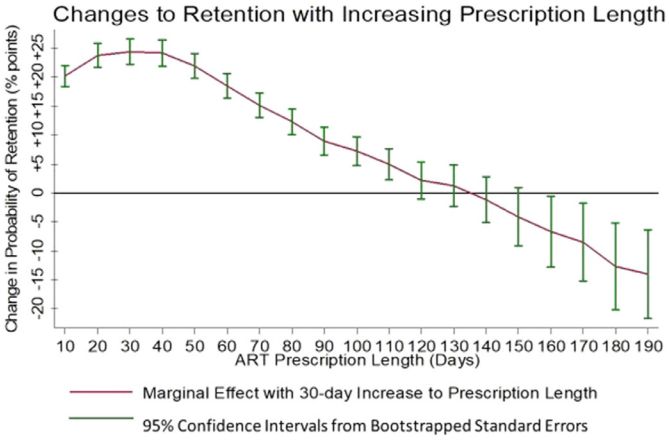

Fig. 1. Changes to retention with increasing prescription length.

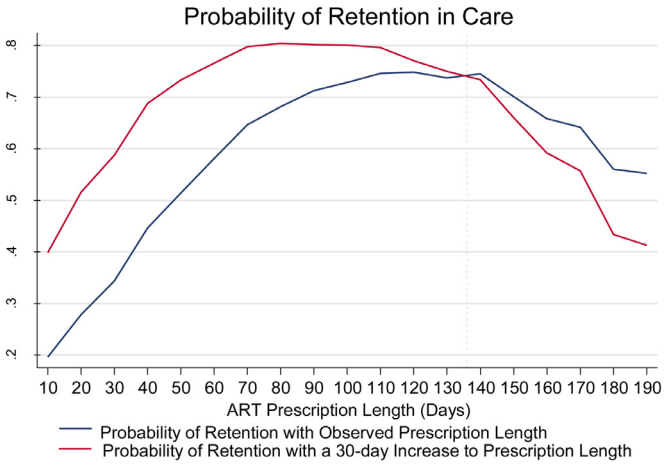

Fig. 2. Probability of retention in care at observed prescription lengths and 30-day increases to prescription lengths.

2.5. Data analysis

To estimate the causal impact of MMD on retention in care, we employed an instrumental variable (IV) analysis using a 2-stage residual inclusion (2SRI) approach for non-linear models [30,31]. IV analysis accounts for unmeasured confounding by using a variable called an instrument that isolates the average direct effect of the treatment or exposure variable on the outcome, independent of the unobserved sources of variability.

The IV approach was used to address potential selection into specific dispensing intervals given that MMD is a treatment strategy that is not randomly applied to individuals; individual-level characteristics likely drive whether a person receives MMD. Further, MMD is person-centered by design, [5, 6, 32] so we would expect individual characteristics to determine exposure to this strategy. However, we do not yet know the direction in which unobserved characteristics affect the likelihood of exposure to MMD or the influence of these characteristics on the relationship of MMD and health-related outcomes, such as ART retention. IV analysis allows us to estimate the causal effect of MMD on outcomes despite non-random assignment to treatment strategies.

The instruments used were the mean and standard deviation of a facility's ART dispensing interval for new ART recipients within the 6-month window in which an individual received their initial ART dispense. Average dispensing intervals (for all people with HIV treated at that facility) vary significantly across facilities represented in the iSanté database. We checked the balance of measured individual-level covariates across levels of the instruments and assessed the strength of the instruments in predicting ART dispensing interval in the first stage model.

Standardized residuals from the first stage treatment model were included in the second stage outcome model along with squared terms for both the residuals and exposure variables to improve model fit. Bootstrapping with 1000 iterations was conducted to achieve valid standard errors with the 2-stage models. We used the Pearson correlation test to assess the goodness-of-fit of the second stage outcome model and to assess any linear relationship between the raw-scale predictions and residuals, and we used the Hosmer-Lemeshow test to plot the mean residuals across deciles of $X\beta$, the product of the data matrix and coefficient vector, and visually inspected whether there were any systematic patterns in the residuals [33], particularly curvilinear patterns not able to be detected with a linear test of model fit.

We calculated the marginal effects on 1-year retention of increasing current, observed dispensing by 30 days with 95% confidence intervals (CI; Fig. 1). Additionally, we graphed the probabilities of retention from the adjusted model at the observed dispensing intervals (observed intervals were rounded to the nearest 10-day increment for graphic illustration), as well as predicted probabilities of retention if current dispensing intervals were increased (Fig. 2). All analyses were conducted in Stata/SE software, version 14 (StataCorp 2016).

Table 1
Characteristics of the study population.

INDIVIDUAL CHARACTERISTICS AND CLINICAL INDICATORS	*N* (%) TOTAL *N* = 21,880
Female	13,595 (62·1)
Age Category, years	
<15	1014 (4·6)
15–24	2838 (13·0)
25–34	6968 (31·8)
35–54	9083 (41·5)
≥55	1977 (9·0)
BMI Category	
Underweight <18.5	3339 (15·3)
Normal weight 18.5–24.9	10, 259 (46·9)
Overweight 25–29.9	2527 (11·5)
Obese ≥30	862 (3·9)
Missing height and/or weight data	4893 (22·4)
WHO Stage	
1	8702 (39·8)
2	5274 (24·1)
3	3180 (14·5)
4	1087 (5·0)
Missing WHO stage assessment and/or relevant data to construct WHO stage from record	3637 (16·6)
Isoniazid for TB management	11,563 (52·8)
Average ART dispensing length in days within first 6 months of treatment – mean (SD)	42·5 (26·3) Range: 6–192
Healthcare Facility (site for ART initiation) Ownership	
Public	8392 (38·4)
Private	8547 (39·1)
Mixed	4758 (21·7)
Not-classified	183 (0·8)

Abbreviations: BMI, body mass index; WHO, World Health Organization; TB, tuberculosis; ART, antiretroviral therapy; SD, standard deviation.

2.6. RECORD statement

This manuscript adheres to the RECORD guidelines for reporting observational studies using routinely collected health data.

2.7. Role of funding source

The funding source had no role in the study design and data analysis. Authors associated with the funding source provided support for the electronic data system, data extraction, and clinical interpretation of the findings.

3. Results

Our analyses included 21,880 HIV-positive individuals. Most participants were women (61·2%) and were aged 25–54 years (73·4%), and almost half of participants (46·9%) had a BMI classified as normal weight between 18·5 and 24·9. Approximately half of the sample population was treated with isoniazid for TB preventative treatment, and most were classified with WHO stage 1 or 2 disease (early HIV/AIDS) at ART initiation. The average ART dispensing interval was 42·5 days (range, 6–192 days; Table 1).

Individual-level covariates were balanced between the instrument levels when the instruments were bifurcated at their medians. The instruments improved balance between the individual-level covariates compared to the treatment variable of ART dispensing interval, suggesting these instruments are valid in this setting. The instruments were highly predictive of individual ART dispensing interval. The second stage, or outcome model, performed well on diagnostic goodness-of-fit tests.

We found that longer ART dispensing intervals for ART-naïve individuals increased the probability of retention at 12 months after treatment initiation. The marginal effect of increasing dispensing intervals was greatest for shorter refill periods, particularly for refills of 60 days or less, though the effect persisted until approximately 110 days. Fig. 1 presents the marginal effects on retention of increasing dispensing intervals by 30 days (i.e., comparing retention outcomes if those receiving 60-day refills were moved to 90-day refills). Estimates above the zero-line indicate an improvement (increase) to retention compared to shorter dispensing intervals by 30 days; estimates below the zero-line indicate detriment (decrease) to retention compared to shorter dispensing intervals. The largest gains were a 24·2%-point gain (95%CI: 21·9, 26·5) in the likelihood of retention with extending dispenses by 30 days for those receiving one-month dispenses. We observed gains to likelihood of retention until approximately 4 months (110 days), +5·1%-points (95%CI: 2·4,7·8). After this point, retention rates did not significantly increase with extensions of the ART dispense; the predicted marginal effect crosses the zero-line at approximately 135 days. Increasing dispensing intervals for those already receiving ≥5-month refills had a potentially negative effect on the probability of retention; - 6·8%-points (95%CI:−13·0, −0·6) at 160-days (Fig. 1).

For observed ART dispensing intervals, we noted that probability of retention in the adjusted models was highest among those with 120-day refills, with the steepest increases to retention occurring between 10 and 90-day refills (blue line in Fig. 2). When we added the marginal effects of a 30-day refill increase to the probability of retention at observed dispensing intervals, retention rates significantly increased for those currently receiving refills less than approximately 135 days, with predicted retention rates highest with 30-day increases to dispense length for those currently receiving 3-month refills (80–90 days). Retention rates did not significantly increase at dispensing intervals >135 days. For individuals already receiving refills for ≥135 days, the probability of retention *decreased* when dispensing intervals were increased, though there is not enough evidence to identify a true negative (or positive) effect due to insufficient power at the right tail of the dispensing interval distribution of this population.

4. Discussion

Our findings suggest that dispensing intervals of 3–4 months for new ART recipients may result in the highest probability of retention at 12 months. The most significant gains to retention occur with increases to ART dispensing intervals for current refills <90 days. We estimated the marginal effect of increasing dispensing interval by 30 days to be beneficial (higher likelihood of retention) until approximately 4 months. We conclude that increasing ART dispensing intervals up to 135 days for new ART recipients shows a clinical benefit in terms of retention in care after 1 year of treatment.

Many guidelines recommend waiting until after 6 months of treatment before starting HIV-positive individuals on MMD [9,22]; however, our findings suggest a clinical benefit to starting MMD soon after ART initiation for clinically stable individuals for whom potential ART toxicity has been ruled out based on clinical judgment. Other studies assessing MMD have used enrollment in treatment for 6 months as an inclusion criterion [5,17], per some country guidelines for MMD [22]. However, ART attrition can be quite high in the beginning stages of treatment [20]. iSanté records indicate that many facilities do not wait until 6 months to allow longer ART dispensing intervals for many ART recipients.

Interpreting causality from an IV regression hinges on the strength of the instrument(s) used in the analysis. Our study's instruments performed well in routine assessments of IV strength. Additionally, pharmacy records in iSanté, which determined ART dispensing intervals, are highly reliable [34] and not subject to major errors in measurement. Regional (or facility) rates of a procedure or medical practice have been used as valid instruments in other studies using IV analysis to assess the casual effect of medical treatments [35]. A possible limitation is that these instruments

could be associated with the outcome of ART retention for reasons other than exposure (dispensing interval). If the facilities that report higher rates of MMD also are more person-centered or sensitive to individual needs—a hallmark of the MMD strategy—this may increase retention in care regardless of ART dispensing interval. Other methodological approaches that do not account for selective selection into longer ART dispenses (such as non-IV methods like generalized linear modeling) could find even larger effects of MMD on treatment adherence, as those who are likely to be adherent may be preferentially given longer medication dispenses. These findings may support the conclusion that MMD is an effective strategy for some ART recipients, but others may need additional and/or alternative strategies to achieve improved treatment adherence. Although our population-averaged treatment effects suggest that most ART recipients would benefit from longer ART intervals up to approximately 4 months, it is very likely that some people living with HIV will need several support strategies to boost treatment success and maintenance.

Our study has several other limitations. As noted earlier, viral suppression is often considered the gold standard for ART success, but viral load test results were not available for the 12-month follow-up visit for many of the study participants at the time of data extraction. Therefore, since we were unable to use this viral suppression outcome consistently across the study sample, we elected for the treatment success proxy of treatment adherence as measured by pharmacy records. We included people with HIV for whom we had complete data for our variables of interest (including retention outcomes, demographics, and key clinical characteristics); individuals with incomplete data were excluded from the analysis. Incomplete clinical data may signal differences in clinical care practices that are associated with both ART dispensing interval and retention in care. The adjustment variables (demographics and clinical characteristics) were chosen a priori based on prior research, as well as conceptual and topical expertise from the research team. The model fit diagnostics supported the inclusion of these variables, though the primary test of model fit, the Hosmer-Lemeshow test [33], does have its limitations. However, this test, coupled with a linear test of correlation between raw-scale predictions and residuals, provided sufficient support for appropriate model fit and the second stage model demonstrated excellent performance with these two tests.

The conclusions from this study are limited to ART-naïve individuals. Due to a small number of people with HIV with refills for >4 months, the confidence intervals of the estimated marginal effects among those with longer ART dispensing intervals are much wider than for the estimates of increasing dispensing intervals for shorter ART refills. We did not assess the effect for increasing ART dispensing intervals for those receiving ART for more than 1 year; in this population, longer ART dispensing intervals may be beneficial. Furthermore, as the uptake of universal HIV testing and treatment guidelines increase in Haiti, the profile of new ART recipients may continue to evolve, and these findings may not be generalizable to future populations in HIV care.

Physician discretion is currently used to determine specific ART dispensing interval in Haiti, which leads to large variation in ART dispensing intervals even among people with similar demographic and clinical characteristics. Our findings can inform policies and individual treatment plans to improve patient outcomes. Communicating about guideline-informed ART dispensing intervals can help bolster provider-patient relationships and enhance the care experience, possibly leading to better retention [36]. Provider-patient communication is a critical component to high-quality clinical interactions [37,38], and this is especially important for HIV-positive individuals, who are involved in lifelong clinical management of their condition.

Our findings also promote using routine data sources to discern valid associative and even causal insights to guide program change. Investing in health information systems has sustainable application for clinical tasks and care management as well as research that can refine these same clinical practices. This research advantage is especially notable during the global COVID-19 pandemic, which has forced clinical practice to adapt rapidly, without the benefit of strong but time-consuming types of evidence such as randomized trials, to changing circumstances to protect patients and providers. Descriptive analyses from iSanté indicate that the mean proportion of ART refills that are >135 days (the point at which we observed a potential detriment to ART retention) have increased for all people on treatment since COVID-19 was confirmed in Haiti. HIV care providers may observe decreased retention rates among new ART recipients in their first year of care who receive ≥4-month ART refills. The desire to limit COVID-19 exposure by increasing ART dispensing length must be weighed against the risk for increased HIV care attrition if ART dispensing intervals are increased beyond 5 months among new ART recipients. Additional efforts outside of the clinic, perhaps through community outreach, to maintain retention for new ART recipients may be warranted, especially during the COVID-19 pandemic with the associated increase in longer ART dispensing intervals.

This study demonstrates a positive effect of increasing ART dispensing intervals on retention in care for new ART recipients. This differentiated care strategy appears to have benefits at care initiation and need not be delayed for 6 months, unless clinically indicated. The largest gains to retention were observed for those receiving ≤3-month refills. There is preliminary evidence that increasing dispensing intervals beyond 4 months could decrease retention, but further research is needed. As longer ART dispensing intervals become more common, it will become feasible to estimate the precise effect of extending dispensing intervals and to assess the point of decreased retention. Extending ART dispensing intervals is an effective service delivery strategy that improves care retention for new ART recipients, especially those with short ART dispensing intervals in settings that have not adopted MMD.

5. Contributors

Canada Parrish, Anirban Basu, Paul Fishman, and Nancy Puttkammer conceived and designed the study. Canada Parrish performed the statistical analysis under the supervision of Anirban Basu and drafted the manuscript with support from Paul Fishman and Nancy Puttkammer. Jean Baptiste Koama, Ermane Robin, Kesner Francois, Jean Guy Honoré, and Joëlle Deas Van Onacker supported the clinical data system and data extraction for the analysis and provided clinical insight for context and the interpretation of the findings. All of the authors revised the manuscript and approved the final version before submission.

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7. Data sharing

Data used in this analysis will not be made available due to protections of medical records data and existing data sharing agreements. Inquiries about the data may be made to the corresponding author. Canada Parrish and Nancy Puttkammer accessed and were responsible for the data associated with this study.

Declaration of Competing Interest

None.

Acknowledgments

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention

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