Duration of Antiretroviral Therapy Adherence Interruption Is Associated With Risk of Virologic Rebound as Determined by Real-Time Adherence Monitoring in Rural Uganda

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Background: Antiretroviral therapy (ART) adherence interruptions have been associated with viral rebound; however, the true risk is unknown because HIV RNA has never been measured during ongoing interruptions.

Methods: The Uganda AIDS Rural Treatment Outcomes Study is an observational longitudinal cohort of adults initiating ART. We monitored adherence with the device that wirelessly transmits records of device openings, and routinely assessed HIV RNA quarterly. When lapses of 48+ hours between device openings were detected, we made unannounced visits to participants to investigate the cause and assess HIV RNA. Generalized estimating equation logistic regressions were used to assess factors associated with viral rebound.

Results: We followed 479 participants (median: 25 months per participant). Most were women (72%), median age was 36 years, median pre-ART CD4 count was 198 cells per microliter, median pre-ART HIV RNA level was 5.0 $\log_{10}$ copies per milliliter, and median duration of prior viral suppression was 13 months. A total of 587 adherence interruptions followed confirmed prior viral suppression, of which 13 (2%) had detectable viral rebound. Viral rebound was associated with duration of adherence interruption (odds ratio: 1.25 for each day beyond 48 hours; $P = 0.007$) and 30-day adherence before the interruption (odds ratio: 0.73; $P = 0.02$).

Discussion: This article is the first demonstration of HIV RNA rebound during adherence interruptions objectively measured in real time. Odds of viral rebound increased by 25% with each day beyond 48 hours. Real-time adherence monitoring was feasible in a sub-Saharan African setting. Further research should assess the potential for real-time adherence interventions to sustain adherence to affordable first-line regimens.

Key Words: HIV antiretroviral therapy, real-time adherence monitoring, viral rebound

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BACKGROUND

Over 8 million people with HIV are receiving antiretroviral therapy (ART) in sub-Saharan Africa.[1] Sustained adherence is critical for achieving and maintaining the viral suppression that allows HIV-infected individuals to lead healthy lives and reduce the risk of HIV transmission to others.[2,3] Adherence estimates in sub-Saharan Africa have generally been high[4]; however, it is not clear if similar levels can be maintained over time.[5–7]

Most adherence studies report a summary measure of adherence (ie, mean or median or a proportion above some threshold of adherence). These measures are insensitive to treatment interruptions and incompletely capture the risk of virological failure.[8,9] For example, 80% adherence could reflect 1 missed dose every 5 days, or it could reflect an 18-day interruption over 90 days. Modern potent ART regimens—particularly those with long nonnucleoside reverse transcriptase inhibitor (NNRTI) half-lives—may be able to "forgive" the former, but not the latter.[8–13] Treatment interruptions have been associated with the presence of drug resistance,[14] and a dose–response relationship has been shown between the duration of adherence interruptions and the odds of viral rebound as measured within the following 28 days.[8]

These findings suggest that interventions that prevent or terminate treatment interruptions may be effective at reducing risk of treatment failure. However, not all interruptions lead to viral rebound; additional data are needed to know the precise relationship between the duration of an adherence interruption and risk of viral rebound. Those data will be central to understanding the risk of treatment failure and timing of potential interventions. Traditional ART adherence measures, including self-report, pill counts, electronic adherence monitors, and drug levels,[15] do not detect problems with adherence

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until weeks to months after they have occurred. Real-time, wireless monitoring strategies have the potential to identify missed doses before viral rebound, thereby prolonging the efficacy of first-line regimens.[16] Preliminary feasibility, acceptability, and validity of real-time adherence monitoring have recently been demonstrated in rural Uganda.[17]

In this analysis, we present data from rural Uganda to determine the relationship between duration of adherence interruption and viral rebound during an interruption using real-time adherence monitoring.

METHODS

Study Setting/Participants

The Uganda AIDS Rural Treatment Outcomes (NCT01596322) study is an observational longitudinal cohort study of adults initiating ART at the Immune Suppression Syndrome Clinic at the Mbarara Regional Referral Hospital in Mbarara, Uganda, which is located approximately 290 km southwest of Kampala. The cohort began in 2005 and had enrolled a total of 750 individuals with 636 active in follow-up at the time of this analysis. Inclusion criteria were age ≥18 years, HIV infection, ART naive at enrollment, and living within 60 km from the clinic. The only exclusion criterion is inability to provide consent. The Immune Suppression Syndrome Clinic provides ART free of charge to approximately 10,000 individuals living with HIV.

Study Procedures

Starting in June 2011, participants who had reliable cellular reception were given wireless ART adherence monitoring devices (Wisepill Technologies, Cape Town, South Africa). This device is a medication container that holds 30–60 tablets. It creates a date–time stamp with each opening that is linked to an anonymous patient identifier and wirelessly transmitted to a study server by general packet radio service (GPRS) or short message service (SMS). Data can be stored in flash memory for later transmission if no network access is immediately available. A "heartbeat" is sent once a day to document device functionality and available cellular network. Battery life is typically 2–3 months. Because <2% of study participants had access to electricity, study staff exchanged expired batteries for recharged batteries during pharmacy refills or other study-related visits.

Routine study visits occurred every 4 months and included measurement of HIV RNA by the standard Roche Amplicor HIV-1 Monitor Test until March 2012 [lower limit of detection (LLD) of 400 copies/mL] and by the Cobas Taqman Test thereafter (LLD of 20 copies/mL). If routine HIV RNA was undetectable consistently for 3 years, the interval between measurements was extended to 8 months.

Opening events from the wireless adherence-monitoring device were assessed on an ongoing basis. To determine the relationship between duration of adherence interruptions and viral suppression, electronic adherence data were surveyed every Monday for ongoing lapses in pill container openings lasting 48+ hours. A 48-hour threshold was chosen as the longest duration with negligible chance of viral rebound on NNRTI-based ART.[9] Surveying for lapses more frequently than every 7 days was not feasible given human resource constraints. Starting in January 2014, the threshold for lapse investigation was lengthened to 96+ hours as a cost-saving measure.

When a lapse of 48+ hours between opening events was detected, a research assistant made an unannounced home visit to investigate the cause, which was categorized as a technical problem (eg, device malfunction, persistent lack of cellular network), missed doses, "pocket doses" (ie, multiple pills removed at 1 device opening for later dosing), or an unclear reason. The categorization was based on a brief interview with the participant and technical assessment of the monitoring device and available cellular network. The participant's reported cause of the lapse was also recorded. If no technical problems were identified, the lapse was classified as an adherence interruption. The research assistant requested a blood sample for HIV RNA determination in all participants with ongoing adherence interruptions, as well as from participants who had resumed taking their ART for <48 hours at the time of the visit (this length of time was felt to be insufficient to result in full resuppression of the HIV RNA). If the interruption had terminated for more than 48 hours, investigations were conducted by phone, if possible, and no blood was drawn for HIV RNA determination.

Statistical Analysis

Data for this analysis were collected between June 5, 2011 and July 31, 2014. Descriptive statistics were used to summarize participant and interruption characteristics. Adherence was calculated as the number of opening event signals received on the study server divided by the number of opening events expected per prescribed dosing regimen during follow-up. Adherence was capped at 100% if device openings exceeded the daily dosage. Device openings by staff and periods where the participant prospectively reported upcoming device nonuse were censored. Lapses lasting more than 30 days with undetectable subsequent routine quarterly HIV RNA were assumed to indicate device nonuse and were also censored.

The association between number of lapses in opening events and months of follow-up was assessed with Spearman rank correlation. For participants receiving real-time adherence monitoring at treatment initiation, we used generalized estimating equation logistic regression analysis to determine the association between adherence categories (<80% and ≥80%) and risk of detectable HIV RNA after initial suppression for each quarter in the first year of treatment. This analysis was limited to participants with wireless adherence monitoring during their first year of ART to assess validity of this adherence measure without the impact of varying prior viral suppression on the adherence-viral rebound relationships (ie, the risk for viral rebound decreases with increasing duration of prior viral suppression).[18–21]

To explore the association between duration of adherence interruptions and risk of viremia during the interruption, lapses in opening events were excluded as follows (Fig. 1): (1) the lapse terminated before a blood specimen could be collected during an ongoing interruption, (2) a known technical

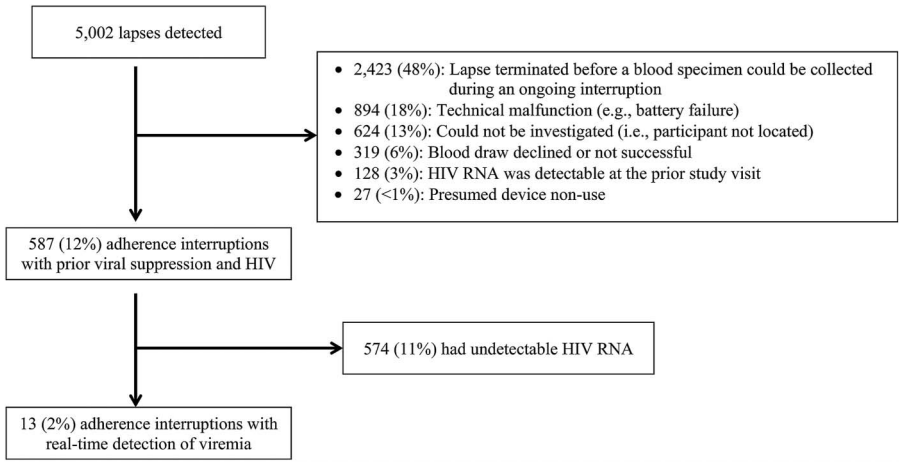

FIGURE 1. Identification of adherence interruptions for the analysis of the relationship between duration of interruption and viral rebound.

malfunction occurred (eg, battery failure), (3) the lapse could not be investigated (ie, participant was not located), (4) the blood draw was declined or not successful, (5) HIV RNA was detectable at the prior study visit, or (6) device nonuse was presumed. The primary analysis consisted of all lapses that could not be attributed to a technical cause; however, a sensitivity analysis restricted to only those interruptions attributed to missed doses by both the research assistant and the participant was also performed. A univariable generalized estimating equation logistic regression analysis was performed to determine the odds of detectable HIV RNA with the following candidate predictor variables: days of interruption duration beyond 48 hours, duration of prior viral suppression (years), 30-day average adherence before the interruption (10% increments), pre-ART HIV RNA ($\log_{10}$ copies/mL) and regimen. Due to the small number of cases of virological rebound, a full multivariable analysis could not be performed. Pairwise multivariable regressions were therefore conducted involving the primary outcome of interest (ie, days of interruption duration) and each of the other variables to determine the stability of the univariable result. The primary analysis utilized an LLD of 400 copies per milliliter. A secondary analysis was also performed using an LLD of 20 copies per milliliter on data collected starting in March 2012. Linearity of the association between duration of interruption and viral rebound was explored with quadratic transformation.

Ethics

Ethics approval for this study was obtained from the Mbarara University of Science and Technology, the Uganda National Council for Science and Technology, Partners Healthcare/Massachusetts General Hospital, and the University of California San Francisco.

RESULTS

Participant Characteristics

A total of 479 participants used the real-time adherence-monitoring device during the follow-up period, providing 902 person-years of follow-up [median of 25 months per participant, interquartile range (IQR): 14–32]. The remaining 157 participants in the cohort were not followed with real-time monitoring because 31 (5%) declined to use the device, 42 (7%) had inadequate cellular network, and 84 (13%) moved outside the study catchment area, making interruption assessments impractical. Most of the cohort were women (N = 344, 72%) and the median age was 36 years (IQR: 29–43). Seventy-eight participants (16%) had no formal education, 279 (58%) had a primary school education, and 122 (25%) had secondary or higher education. The median time to clinic was 45 minutes (IQR: 30–60). The median pre-ART CD4 count was 198 cells per microliter (IQR: 110–295), median pre-ART HIV RNA level was 5.0 $\log_{10}$ copies per milliliter (IQR: 4.5–5.5), and median duration of prior viral suppression was 13 months (IQR: 3–48). The ART regimen included nevirapine for 205 (43%) participants, efavirenz for 244 (52%) participants, and other for 25 (5%) participants.

Overall Adherence and Association With Routine Detectable HIV RNA

Over the total analysis period, adherence for the cohort of 479 participants was a median of 86% (IQR: 73–94). As shown in Figure 2, detectable routine quarterly HIV RNA was significantly higher among participants with <80% adherence as observed by real-time adherence monitoring during their first year of ART [N = 237; 14% versus 5%; OR for <80% adherence: 2.04 (95% CI: 1.19 to 3.47); $P = 0.009$].

Opening Event Lapse Characteristics

A total of 5002 lapses of 48+ hours between opening events were detected in the cohort. The median duration was 3 (IQR: 2–5) days, and the median number of lapses per participant was 1 per month (IQR: 1–2). The number of lapses per participant was stable over time, with a possible trend toward a decline in lapses (Spearman rho = −0.035, $P = 0.09$). Causes of lapses are given in Table 1. The number of reported causes per lapse was 1 for 84% of lapses (N = 4190),

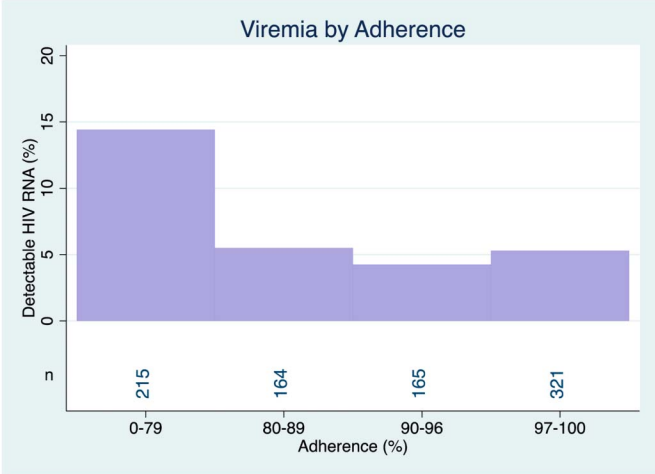

FIGURE 2. Association between detectable routine HIV RNA (collected quarterly) and overall adherence for participants in their first year of ART [N = 237; OR for <80% adherence 2.04 (95% CI: 1.19 to 3.47); $P = 0.009$]. Adherence is shown as quartiles.

2 for 3% of lapses (N = 168), and 3 for <1% of lapses (N = 4). The cause was missing for 640 (13%) of interruptions. Categories of lapse causes (ie, technical problem, missed doses, pocket doses, and unclear) were relatively evenly split per the research assistant, whereas participants most commonly reported an unknown cause (50% of lapses).

Figure 1 indicates how lapses were selected for the analysis of the relationship between adherence interruption duration and viral rebound. A total of 587 (12%) investigated adherence interruptions followed confirmed prior viral suppression among 261 of the total 479 participants (54%). The median duration was 4 days [IQR: 3–5, $P < 0.001$ in comparison with the median duration of 3 days (IQR: 2–5) for the 4415 uninvestigated lapses]. Of these, HIV RNA was collected on the same day the interruption completed in 278 (47%), within 48 hours of the interruption completion in 306 (52%), and before the interruption ended in 3 (1%). In those 3 interruptions, the duration of time between investigation and end of the interruption was 7 days or less. Viral rebound was detected during 13 (2%) interruptions.

Relationship Between Duration of Adherence Interruption and Viral Rebound

The incidence of detectable HIV RNA during the interruption increased with increasing duration of interruption up until 14 days in the 587 adherence interruptions with prior viral suppression (Fig. 3). This relationship was found to be linear. At least 5% of interruptions lasting longer than 7 days had detectable viremia (median: 3018 copies/mL; IQR: 797–24,401). Twenty-one interruptions (3%) were longer than 14 days, none of which had detectable HIV RNA during the interruption or with the subsequent routine HIV RNA measurement (2 HIV RNA levels were not available at the time of analysis). The primary cause of these interruptions was reported as unknown or pocket doses for all but 1 (96%), which was attributed to missed doses. Of the 13 interruptions in which viral rebound occurred in the primary analysis, 10 of 12 (83%) were suppressed at the follow-up routine HIV RNA (one HIV RNA level was not available).

In univariable regression analysis (Table 2), viral rebound was significantly associated with the duration of interruption (OR: 1.25 for each increasing day of interruption length beyond 48 hours; 95% CI: 1.06 to 1.47; $P = 0.007$) and 30-day adherence before the interruption (OR: 0.73 for each 10% increase in adherence; 95% CI: 0.55 to 0.96; $P = 0.02$). Trends were seen for an association with prior duration of viral suppression (OR: 0.75 per year; 95% CI: 0.52 to 1.08; $P = 0.12$) and use of an efavirenz versus nevirapine regimen (OR: 0.41; 95% CI: 0.13 to 1.32; $P = 0.14$). No effect was seen with pre-ART HIV RNA. The 20 interruptions lasting greater than 14 days that had undetectable HIV RNA during the interruption and at subsequent routine HIV RNA measurement and did not have a primary cause of missed doses were presumed to indicate device nonuse and were excluded from the regression analysis. In pairwise multivariable regression models limited to

TABLE 1. Causes of 48+-hour Lapses Between Device Opening Events per Research Assistant and Participant Opinions

	Participant Opinion				
Research assistant opinion	**Technical Problem**	**Missed Doses**	**Pocket Doses**	**Unclear**	**Total**
Technical problem	**226**	18	15	669	928
Missed doses	17	**924**	68	268	1277
Pocket doses	9	25	**946**	74	1054
Unclear	70	21	19	**1368**	1478
Total	322	999	1048	2379	

Values in bold indicate concurrence of opinion (79% of all causes). More than 1 cause was identified for some lapses; column and row totals are therefore not equal.

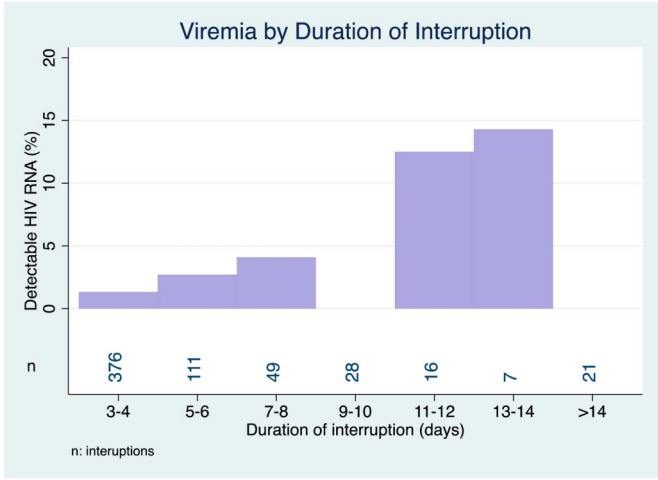

FIGURE 3. Association between duration of adherence interruption and viral rebound. A total of 587 interruptions were seen among 261 of the total 479 participants (54%). Viremia exceeded 5% of interruptions lasting longer than 7 days. Twenty-one interruptions (3%) were longer than 14 days, none of which had detectable HIV RNA during the interruption or at the subsequent routine quarterly assessment.

the primary variable of interest (ie, duration of adherence interruption) plus each other variable, the association between duration of adherence interruption and viral rebound was stable with OR ranging from 1.22 to 1.27 for each increasing day of interruption length beyond 48 hours (all were significant with a maximum $P = 0.02$). In the sensitivity analysis limited to the 248 interruptions attributed to missed doses by both the research assistant and the participant, findings were similar with an odds of viral rebound of 1.53 for each day beyond 48 hours (95% CI: 1.15 to 2.03; $P = 0.003$), although the number of interruptions with rebound viremia was low at 4 (2%).

In another secondary analysis using an LLD of 20 copies per milliliter for both the level of HIV RNA before the interruption and during the interruption (N = 183 participants), 313 adherence lapses were identified with a median duration of 3 days (IQR: 3–5). Of these, 62 were detectable (median: 38 copies/mL; IQR: 26–58). The only significant association seen in univariable regression analysis between duration of adherence interruption and viral rebound was with pre-ART HIV RNA (OR: 1.66 for each $\log_{10}$ copies/mL, $P = 0.02$).

DISCUSSION

This article is the first demonstration of HIV RNA rebound during adherence interruptions objectively measured in real time. The odds of viral rebound increased by 25% with each day beyond 48 hours, and detection of viremia exceeded 5% of interruptions lasting longer than 7 days. These findings are consistent with Genberg et al,[8] who found that objectively measured interruptions independently predicted HIV RNA rebound, controlling for average adherence between interruptions. In that study, interruptions of 7–14 days in regimens based on NNRTIs were associated with increased odds of detectable RNA (OR: 1.91; 95% CI: 1.10 to 3.33) as measured within 28 days compared with no 48+-hour interruptions. The lack of viremia seen in this study after 14 days (both during the interruption and at subsequent routine quarterly HIV RNA measurement) suggests device nonuse, rather than a lack of association between viral rebound and longer duration of adherence interruption.

The lack of association between duration of adherence lapse and viral rebound seen in the subset of interruptions assess LLD of 20 copies per milliliter suggests that low-level variations in HIV RNA may not be related to adherence. Alternatively, longer interruptions may be needed before viral replication begins at such low levels. This article also establishes the feasibility of real-time adherence monitoring among nearly 500 participants in a rural sub-Saharan African setting, although 5% declined its use and 7% could not use the device due to poor network. Of the 5002 48+-hour lapses identified, only 624 (13%) could not be investigated. While technical problems did cause approximately 20% of the lapses, ongoing monitoring was still possible. Most technical problems were due to low battery voltage or modem failure in the setting of poor cellular network. The battery life in these devices has recently been extended to 6 months with device modifications, and modem upgrades have nearly eliminated data transmission failures. These improvements should eliminate the major technical barriers to real-time adherence monitoring seen in this study.

The other relationships between HIV RNA levels and adherence found in this study support prior findings and add to the evidence for validity of real-time adherence monitoring. We found a strong relationship between <80% adherence and detectable HIV RNA consistent with prior studies finding reliable viral suppression between 80% and 100% with potent

TABLE 2. Predictors of Viral Rebound During an Adherence Interruption. Viral Rebound Was Observed During 13 (2%) of 587 Adherence Interruptions

	Univariable OR (95% CI)
Duration of adherence interruption (each day beyond 48 h)	**1.25 (1.06 to 1.47; *P* = 0.007)**
30-d adherence before interruption (each 10% increase)	**0.73 (0.55 to 0.96; *P* = 0.02)**
Prior duration of viral suppression (yrs)	0.75 (0.52 to 1.08; $P = 0.12$)
Regimen—nevirapine	Ref
Efavirenz	0.41 (0.13 to 1.32; $P = 0.14$)
Pre-ART HIV RNA ($\log_{10}$ copies/mL)	1.28 (0.66 to 2.49; $P = 0.47$)

Values in bold indicate statistical significance ($P < 0.05$).

ART. While summary measures of adherence incompletely capture the risk of virological failure, they are useful for comparing our findings with those of other studies and for establishing a minimum level of validity. We also confirmed that the risk of viremia declined over time with increasing duration of prior viral suppression.[18–21] Additionally, the trend toward lower risk for viral rebound with efavirenz versus nevirapine is consistent with the longer elimination half-life of efavirenz (ie, 40–55 versus 25–30 hours).[22]

The strengths of this analysis include the large number of participants and median duration of follow-up of more than 2 years. The primary limitation is the small number of participants with virological rebound identified during interruptions. Additionally, adherence monitoring and home visits to investigate potential lapses may have increased adherence overall, reduced the frequency of adherence interruptions, and/or terminated adherence interruptions that otherwise would have lasted longer. We were also unable to investigate all interruptions that took place during this study; it is therefore possible that we did not detect some cases of rebound viremia (eg, those that may have resolved before a research assistant could visit the participant) that could have influenced our analysis. However, the duration of uninvestigated interruptions was significantly shorter than those investigated, making the likelihood of viral rebound lower. Additionally, the classification of all lapses not due to technical causes as adherence interruptions was a conservative approach; lapses attributed to pocket doses and unclear causes may not have been true adherence interruptions. Because the accuracy of self-report is unclear, and missed doses tend to be underreported,[23] findings in our analysis are biased to the null. Importantly, findings in the sensitivity analysis limited to lapses attributed to missed doses by both the research assistant and the participant were similar.

While the main goal of this study was to determine the relationship between duration of adherence interruption and viral rebound, the study procedures necessary to accomplish this goal also demonstrated that real-time adherence intervention is possible. Importantly, nearly half of the adherence interruptions concluded with the investigation. This finding suggests that a real-time adherence intervention could lead to resuppression for many individuals with adherence challenges, although the study design did not allow us to determine a causal relationship between interruption visits and viral resuppression. Moreover, some instances of viremia could spontaneously resolve. Further studies involving randomized trials of real-time adherence intervention with adherence, and virological outcomes are therefore needed. Our data indicate that the most critical time for intervention may be within 7 days. The acceptability of real-time monitoring has been established previously,[17] but unique concerns may arise with real-time intervention and should also be considered.

While real-time adherence monitoring is currently expensive, manufacture of these devices at scale will likely lead to significant reductions in cost as is commonly seen in technology development. The financial feasibility of real-time adherence monitoring is further supported by recent findings that electronic monitoring can lead to significant cost saving in laboratory monitoring in a resource-rich setting.[24] These findings combined with the success of several recent interventions using mobile technology to promote ART adherence[25,26] present support for use of real-time adherence interventions to be delivered where and when they are most needed. Further research is needed to assess the potential for real-time adherence interventions to sustain adherence to affordable first-line ART regimens in sub-Saharan Africa and other developing settings.

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