Title of the study

INcentives and ReMINDers to Improve Long-term Medication Adherence (**INMIND**)

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Introduction

Antiretroviral therapy (ART) has transformed an HIV infection from a likely death sentence to a manageable chronic condition [1], but the efficacy of ART hinges on maintaining high (at least 80-85%) mean medication adherence [2–4]. Globally, roughly 53% of people living with HIV (PLHV) have access to ART, but only 44% of PLHIV are virally suppressed [5]. In Sub-Saharan Africa, only a quarter of PLHV are virally suppressed [5], which results in avoidable cases of drug resistance [6] and death [7]. Structural (e.g., drug availability), social (e.g., stigma), and economic (e.g., distance to clinic, clinic fees) ART adherence barriers have been documented in the literature [8–10], but patient behavior has been identified as a key factor determining the lack of viral suppression [11]. Recent research has shown that mean ART adherence ranges from 60-80% in Uganda, and only 30-60% of patients achieve 85% adherence [12–14]. Thus, novel behavioral interventions are needed to help establish and maintain high ART adherence habits among PLHIV in Uganda.

Daily habits (or routines) are a commonly reported strategy for maintaining high medication adherence among patients who successfully manage chronic diseases [15,16], but forming new routines is often difficult for patients to do on their own. According to recent psychology research, it takes approximately three months of repeatedly performing a daily behavior in response to the same contextual cue [17–20], as outlined in the Habit Formation Model in Figure 1a [21], before the behavior becomes routinized. Once routinized, the cognitive processes that govern the behavior move to neurological systems that operate non-consciously [22–25]. Additionally, behaviors that are routinized no longer require high intrinsic motivation to be carried out, and thus can enable even the most vulnerable ART treatment initiators, such as those with limited motivation, to maintain high long-term adherence.

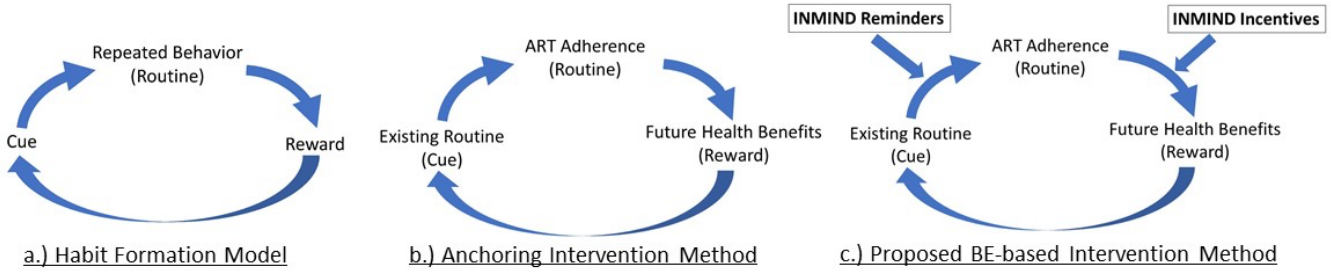

Figure 1: Duhigg's (2013) habit formation model underlies the anchoring intervention strategy, which we propose to enhance in INMIND through incentives and reminders to successfully routinize ART adherence among HIV-patients.

One common intervention method for establishing new routines is to anchor the targeted behavior to an existing routine that acts as the contextual cue. For example, taking ART medication after brushing one's teeth in the morning or after completing evening prayers. This method is often called Anchoring (Figure 1b), and has been shown to be an effective intervention for promoting physical activity routines [26], improving dietary routines [27], and maintaining smoking cessation [28]. However, these existing studies typically enrolled participants with high intrinsic motivation for the targeted behavior [29–33], and therefore hold little potential for real-life clinical situations where there is no extra support for individuals with low intrinsic motivation (as is typical for many patients in HIV care [34]). Moreover, less than half of participants in these existing studies successfully used their anchor and maintained the desired behavior in the long run [35].

Behavioral economic theory demonstrates the need for ongoing support during the time it takes to complete the routinization process and also provides proven intervention methods for delivering such support to enhance existing anchoring interventions. The behavioral economic biases of lack of salience of ART adherence (e.g., over time, more pressing needs of daily life dominate one's attention and focus) and present bias (e.g., excessively undervaluing the future health benefits of one's actions) help to explain why many people have trouble sticking to their healthy intentions [36,37]. Fortunately, behavioral economics also suggests two methods for countering these biases: 1. text messages that can be used to reinforce information provided at recruitment and to increase the salience of the anchoring routinization strategy, and 2. small behavioral economics-based incentives that have successfully changed a range of health behaviors by countering present bias [38–41]. Therefore, this study will test whether incentives for linking daily pill-taking to the timing of an existing routine behavior can establish and maintain high ART adherence routines in a feasible and scalable manner.

Additionally, this intervention is being targeted to treatment initiators in order to leverage the 'fresh start'-effect [45], a period of heightened motivation and attention. ART adherence instructions are initially salient for treatment initiators, but over time they fade from attention. Among HIV-infected adults in Sub-Saharan Africa, forgetfulness is the most frequently reported adherence barrier to maintaining high long-term adherence [46,47]. Treatment initiators may therefore need subsequent support for adhering to the ART medication protocol until the behavior has been successfully routinized, which will be provided in the form of text messages and incentives.

We propose to test the intervention “INcentives and ReMINDers to Improve Long-term Medication Adherence” (INMIND) in a pilot, parallel group randomized controlled trial (RCT) at the Mildmay Uganda HIV clinic in Kampala, Uganda with two intervention groups and a control group using an even allocation ratio of 1:1:1 between the three study groups. All participants (including in the control group) will receive information about the importance of behavioral routines, as is part of the standard adherence counseling for treatment initiators at Mildmay Uganda and will create personalized ART adherence anchoring strategies. The first intervention group will additionally receive text message reminders of their anchoring strategy, and the second intervention group will receive both the text message reminders and small incentives conditional on taking ART pills within a time window that corresponds to participants’ personalized anchoring strategy. We hypothesize that the text message reminders and incentives will increase participants’ use of their anchoring strategy, and thus medication adherence will be better maintained after the intervention ends in our two intervention groups relative to the control group. We also expect to see stronger maintenance in the intervention group receiving both reminder messages and incentives than the intervention group receiving only reminder messages.

Methods

Ethics Approval

This pilot RCT has been funded by the National Institutes of Mental Health in the United States (R34MH122331) and approved by the RAND Human’s Subjects Protection Committee (2020-N0632), Mildmay Uganda Research Ethics Committee (MUREC) (0701-2021), as well as the Uganda National Council for Science and Technology (HS128ES). As of February 18, 2022, recruitment was completed.

Study Design

This study will use a three-armed randomized controlled trial (two intervention groups and one control group) with randomization at the individual level. The interventions will be administered for a period of three months from the baseline survey. During the intervention period, MEMS data readings will be collected monthly, wherein prize drawings for eligible participants in the Incentives group will be carried out. Since the population of interest are treatment initiators, the monthly study visits are expected to coincide with the monthly clinic visits as mandated for

newly diagnosed clients who are getting accustomed to ART treatment. During the post-intervention period, the team will follow participants and continue MEMS data collection during the participants' regular clinic visits (expected to be every month for the first six months post treatment initiation, and every one-to-three months thereafter) for a period of six months, bringing the total study period to nine months.

Since the long-term goal of the study is viral suppression, viral load data will also be collected during the routine assessment. Viral load tests for treatment initiators are conducted after the first six months of ART initiation, and then switched to 12-month periods as per clinic and Ugandan Ministry of Health guidelines. Survey assessments will be administered at baseline, month three, and month nine for all participants.

It is important to note that the pilot study is being preceded by a formative phase, and succeeded by an adaptation phase, both of which are geared towards collecting qualitative data pertaining to the overall design, feasibility, and acceptability of the interventions. The results of the formative phase will be used to adapt the pilot intervention materials and timeline prior to the intervention administration. The adaptation phase is expected to provide feedback on the mission critical parameters of the interventions, which would be utilized to mold the intervention in preparation for a full-scale randomized controlled trial. Figure 2 gives the timing of study activities.

Study Sites

The study will be performed at the Mildmay, Uganda, an HIV clinic in Kampala, Uganda. This clinic specializes in providing comprehensive HIV and AIDS prevention, care, and treatment services to over 105,000 HIV-infected patients. It offers integrated health services to a diverse population base; of the 15,000 patients served at the main site in Lweeza, 11% are children younger than 18 years, 65% are female, and 100% of patients are on ART. Mildmay also has well-established electronic medical records infrastructure, making it one of the growing number of facilities using electronic medical record systems in Uganda.

Apart from the patient-facing work, Mildmay also provides technical assistance to organizations and governments, hosting training and educational courses for over 1,500 professionals per year. Further, the Mildmay Uganda laboratory is accredited by the South African National Accreditation System under ISO 15,189:2012, and specializes in virology and other tests.

Mildmay also has numerous ongoing research projects involving international researchers. It has a standing Community Advisory Board comprising of church leaders, elected councilmen, healthcare providers (external to Mildmay), and HIV client advocates.

Sampling Strategy

The objective of this study is to establish preliminary efficacy as well as acceptability and feasibility of the interventions. Consequently, 150 participants will be recruited from Mildmay's main site for the pilot study. The sample will be representative of the patient population at Mildmay with a roughly 70:30 ratio of female to male clients.

Electronic medical records and the hospital electronic database will be used to screen the client population for initial eligibility based on age and ART initiation period, as noted in the Eligibility Criteria below. For this step, the hospital staff (and not the study coordinator) will mine the electronic database for this information to create a master list of eligible clients. Given the focus on treatment initiators, this process will be carried out weekly to identify newly diagnosed clients who are eligible to participate in the study.

A daily list of expected clients will be generated from the master list for the study coordinators to locate those deemed eligible and who are due for a clinic visit. Once a client is located, a pre-baseline visit will be initiated with the study coordinator approaching the client and inquiring about their interest in participating in an ongoing study. On confirming interest, clients will be taken to a separate study room to verify their eligibility, and to receive their consent to participate. Consented participants will be given a medication event management system (MEMS) cap and instructed to store one of their HIV medications in a pill bottle with the MEMS cap attached. Additionally, they will be given a study appointment after approximately one month of this initial visit for adherence data retrieval and baseline survey administration. The first month of adherence data will be used as a baseline and the intervention will not begin before this follow-up visit.

Inclusion Criteria

The study sample will consist of male and female clients aged 18 and older who have started ART at Mildmay within the preceding three months. Treatment initiation is an important eligibility criterion given the conceptual framework of the pilot, which suggests that habit formation during initiation is a key driver for sustained ART adherence over time. Based on electronic records

data from Mildmay, each month at least 100-150 clients with these characteristics begin treatment at the hospital (for a total of 1,758 in 2018); therefore, a large pool of potentially eligible clients will be available for recruitment. Given the nature of the intervention, inclusion will also require participants to own, or have access to a phone at least five days a week throughout the duration of the intervention, while being willing to receive text messages throughout the intervention period.

Exclusion Criteria

Children under the age of 18 were excluded for two reasons: 1) the pediatric clinic is separate from the main recruitment site (which primarily caters to adult clients), and 2) the intervention might require alteration to account for the specific needs of children and adolescents. Additionally, clients who are not mentally fit to understand the consenting or study procedures, as well as clients who speak neither English nor Luganda (the local language spoken by the majority of people in and around Kampala) were excluded. As both intervention groups rely on the receipt of text messages, clients who don't own a cell phone or have access to one will also be excluded.

Participation in another adherence study as well as non-ability or non-desire to use MEMS caps regularly throughout the course of the study will also be a basis for exclusion. Consequently, if the baseline MEMS reading suggests that participants opened their pill bottle less than 30% of days, and if that was not a consequence of low adherence, then the participant will be given a transport refund and will be unenrolled from the study. Finally, clients coming outside regular clinic working hours will be excluded.

Randomization and Allocation

Participants will be randomly assigned to either one of the treatment arms (T1 = *Messages*; T2 = *Incentives*) or the control arm after consenting but will only be informed of their assignment after the baseline survey is over to minimize any potential influence of the assignment on the baseline survey responses. The distribution ratios for the randomization will be 1:1:1 and the assignment will be carried out through a computer-generated randomization component built into the baseline survey administration software, called Questionnaire Development System. The random assignment (to either the control group or one of the two intervention arms) will be revealed at the end of the baseline survey to both the participant and the study coordinator, who will therefore not know the respondent's treatment assignment during the survey. Given the

nature of the intervention, neither the interviewers nor the participants can be blinded to the treatment status. However, the data analyst who will conduct the impact analysis will be blinded to treatment assignment.

Procedures

Interventions

The pilot will include a control arm, along with two intervention arms – *Messages* (T1) and *Incentives* (T2).

Control Group: Usual Care

Participants assigned to this arm will receive care as usual, including the adherence support mechanisms that are part of usual care practices. At recruitment, participant will be educated about the importance of pill-taking using a leaflet that details information on how to establish healthy pill-taking routines. Participants will then be asked to select one of the following three pill-taking anchors: getting dressed in the morning, eating a meal (breakfast) in the morning, or eating dinner in the evening, which will also be described in a habit leaflet, and they will be asked to specify the time at which their anchor typically occurs. Once selected, participants will be asked to continue using their MEMS caps and to bring the caps during the next visit.

During each of the subsequent study visits, scheduled roughly one month apart during the intervention period and 1-3 months apart subsequently, participants will be asked a short questionnaire inquiring about changes in their ART adherence behavior, including any changes in location, times, and social activities surrounding their pill-taking behavior and their ART adherence habit strength. They will also be asked about any clinical changes to their ART regimen, as well as about their daily MEMS cap usage. This is because pill-pocketing (dispensing of more than one dose in a given bottle opening event) is a common phenomenon among the population, with 15% of a previous study sample reporting pocketing [48]. If participants indicate pocketing, the study coordinator will work with the participant to find another solution to avoid pocketing and continue using their MEMS cap, and we will adjust for their pocketing in our assessment of their adherence outcomes. Finally, participants will be asked about any changes to their contact information or addresses, and updates will be noted in the contacts data.

The study coordinator will then download the readings from the MEMS cap, inquire about the participants' next visit, and remind them to continue taking their pills on time. This procedure will be carried out throughout the intervention and post-intervention periods.

Treatment Group 1: Messages Group

Participants assigned to this arm will receive daily text messages in addition to care as usual during the three-month intervention period. When the participant is informed of their treatment assignment, they will be educated on the same habit leaflet as all other study groups and asked to pick an anchor and share the time of the day the anchor typically occurs. In addition, the study coordinator will register the participant's cell phone number along with their language preference for text messages (English or Luganda) on an online text messaging system, Twilio. The system will include programmed text messages that will be sent to all participants at 2pm local time every day for the three-month intervention period. Table 1 shows some example text messages, each of which would be sent on a specific day of the week. Once registered, the study coordinator will send the participant a test message to confirm registration. If for any reason the participant is unable to confirm receipt of the test message (for example, if their primary number is owned by another person that they live with), the study coordinator will try registration again. If the registration is still not confirmed, the participant will be unenrolled from the study.

Table 1: *Example Text Messages for the Messages and Incentives Groups*
Hello, this is INMIND. Take your vitamins together with your existing routine for good health!
Hello, this is INMIND. Forming routines requires effort now but will pay off in the end!
Hello, this is INMIND. Don't forget to take your vitamins every day at the same time!
Hello, this is INMIND. Remember to stick with your healthy plans!

During each subsequent intervention-period study visit for the enrolled participants, participants will be asked about the text messages in addition to the questions asked to the participants in the control group. Specifically, participants will be asked whether they have been receiving the text messages and whether they read them. MEMS data will also be downloaded during each of these subsequent clinic visits.

Treatment Group 2: Incentives Group

Participants assigned to this arm will receive monetary incentives in addition to daily text messages (as with the *Messages* arm) and care as usual, during the three-month intervention

period. Upon revealing their group assignment, participants will be registered on the Twilio platform following the same procedures as outlined for the *Messages* arm. Participants will also be informed that if at their next visit they have taken their medication on 70% or more of the last 30 days within +/- one hour of their chosen anchor time, then they will be eligible to participate in a lottery to win mobile airtime. The study coordinator will note that they will receive three opportunities to participate in the lottery (i.e. at each study visit over the next three months, if they are eligible). To ensure participants understand the process, the study coordinator will carry out a mock prize drawing wherein participants will choose from one of three cards listing an airtime prize amount. The chosen card and corresponding prize will be revealed to the participant, and the amount listed on the card will be sent to the participant's phone number (via Reloadly) in the form of a mobile top-up balance.

During each subsequent study visit, the study coordinator will check the client's MEMS cap data and fill out a form that asks questions about adherence behaviors (as with the control group), and text messages (as with the Messages group). The study coordinator will also ask about pill pocketing to assess prize eligibility. To avoid unfairly punishing participants who pocket doses (resulting in an under-reporting of MEMS data in the software), participants will be asked about an estimated number of doses pocketed and will be allowed to enter one wild card prize drawing when they did not reach the adherence threshold. They will be specifically informed that this will be a one-time exception. After the three-month intervention, participants will follow the same procedures as the Control and Messages groups.

MEMS-cap procedures

The MEMS caps will be used to assess the primary outcome measures – mean monthly adherence during intervention and post-intervention and a novel adherence measure assessing the timeliness of adherence during the intervention and post-intervention periods. The caps will be distributed to all participants regardless of their group assignment so as to avoid any spurious intervention effects associated with the cap use. The data captured by these caps will be downloaded at each clinic visit using a MEMS cap reader that will be connected to a study computer, and we will use these data to construct our participant-day-level measures of ART medication adherence.

The study coordinator will assist the patient with dispensing their medication into a bottle we provide with an attached MEMS cap, or, if preferred by the patient, they can put the MEMS cap

on the medication bottle provided by the clinic. We will monitor adherence to only one daily dose of antiretroviral medication as studies show that rates of adherence do not differ significantly across medications taken by an individual patient [49]. All participants will be asked to use their MEMS cap continuously throughout the study and return with the cap and their pill bottle for each clinic visit. Participants will be informed that the cap records when the bottle is opened. They will also be informed that these data will not be shared with clinicians.

			Months								
	Enrolment	Allocation	Post-allocation			Post-Intervention/Closeout					
TIMEPOINT	-1	0	1	2	3	4	5	6	7	8	9
ENROLMENT:											
Eligibility screen	X										
Informed consent	X										
MEMS-Cap Given	X										
Allocation		X									
INTERVENTIONS:											
T1: Messages		X	←	—	→						
T2: Incentives		X	←	—	→						
ASSESSMENTS:											
MEMS-Cap Measured Adherence		X	←	—	—	—	—	—	—	—	→
Participant Surveys		X			X						X
Viral Load		X			X						X

Figure 2: Schedule of enrolment, interventions, and assessments (SPIRIT Figure)

Study Timeline

Recruitment

The recruitment (or pre-baseline) visit will be used as an opportunity to screen the clients. Once the client is found to meet the initial eligibility criteria, s/he will be given a MEMS cap, which will be used to track baseline adherence and study eligibility for approximately one month. In case their clinic visit does not coincide with the expected study visit, participants will be provided a study visit appointment and will be told that they will receive travel compensation for making the additional trip. Clients will also be consented to participate during this initial recruitment visit.

Months 1-3 Visits

During the three-month intervention period, participants will be schedule for monthly clinic appointments and the study coordinators will a) collect information on changes or degradations of existing routine behaviors; b) conduct prize drawings with the *Incentive* group; and c) update contact information in case phone numbers or addresses have changed. After the first three months, this information will be collected during the participants' regular clinic visits. When participants report the degradation of their selected behavioral anchor, a new daily routine will be identified for the anchoring strategy from the suggested list of three common routine behaviors.

Post-Intervention Surveys

Follow-up surveys will be administered at month three (i.e., at the end of the intervention) and month nine (i.e., six months after the end of the intervention) to evaluate behavioral persistence. These surveys will be designed to evaluate how the intervention affects both the primary outcomes and secondary outcomes, as well as cognitive and motivational factors that may be influenced by the intervention. Intervention effects over the nine-month study period will also be assessed as these effects might be most pronounced in the first months when the pill-taking routine is first established but then taper off as the novelty of the intervention fades or anchoring routines are changed. The post-intervention assessment will happen during a scheduled hospital visit to avoid participants having to make costly additional hospital visits specifically for interviews.

Data Collection Methods

Surveys

The baseline survey contains questions pertaining to:

1. *Demographics and socioeconomic status*, including age, gender, education, relationship status, employment type and status, income, preferred language, housing, economic shocks, food insecurity, and household composition
2. *Attitudes and beliefs about HIV medication*, including adherence behaviors and perceived benefits, and community perceptions around pill-taking
3. *Sources of motivation* for medication adherence, for example, reduction in HIV transmission, maintenance of good health and ability to look after family, and/or maintenance of good physical appearance

4. *Habits* associated with regular pill-taking, including pill-taking routines, missed doses and reasoning (to assess any perceptual and structural barriers to pill-taking), and costs associated with prescription fills. This would be assessed using the Self-Reported Behavioral Automaticity Index [50], which is a validated subset of the Self-Reported Habit Index [51] that measures the automaticity of performing a specific routine behavior based on responses to four questions (e.g., "taking my medication is something I do without thinking") on a 7-point Likert scale from "strongly disagree" to "strongly agree."
5. *Healthcare information*, including perceptions on health since initiating ART initiation, and over the past month

In addition, a measure developed by Falk et. al. will be used to assess risk and time preferences, altruism, trust, and positive and negative reciprocity, on a scale of 0-10, where 0 means "completely unwilling to take risks" and 10 means "very willing to take risks" [52]. Additionally, the Intrinsic Motivation Inventory will be used to examine participants' subjective motivation for taking medications [53]. The three-month and nine-month surveys will additionally include questions assessing comfort with using the MEMS caps, the acceptability of the text messages and prize drawings, and overall study satisfaction. Upon completing each survey, participants will be given 30,000 USh (~$8.25 USD) as travel compensation.

MEMS Data and Access Forms

The MEMS data will be automatically downloaded and stored electronically using the MEMS cap software that will be installed on a tablet accessible by the study coordinator. The other study data, including participants' survey responses, monthly visit reports, and other information about study dropout, will be recorded by study personnel in Microsoft Access templates designed by the research team. These electronic data will be safely stored at Mildmay and securely transferred to the research team in the United States periodically during the study period, and at the end of the nine-month study.

Chart Abstraction

Participant's viral load will be used as a complementary measure to the MEMS data for the assessment of ART adherence. They are now a part of routine clinical care at Mildmay with tests carried out when someone receives a positive HIV test result, after six and 12 months of the initial diagnosis, and every 12 months thereafter. Consequently, the results of the viral load

test will be chart abstracted and the data abstraction will be timed with the routine tests for the participants.

Participant Tracking

Extensive tracking information will be collected at recruitment and will be verified at each study visit. This will include mobile phone numbers, home address, and email addresses, as well as the contact information for two individuals who live in the same community and who the participant is comfortable and familiar with. These additional contacts are collected to ensure that the participant can be located in case their contact information changes. These procedures have limited attrition in the researchers' previous studies to about 5% [44,48].

If a participant in either treatment group loses, breaks, or otherwise cannot use their mobile phone, then they will no longer be able to receive text messages as part of the intervention. To respond to this possibility, the study coordinator will record the functionality of participants' mobile phones at each monthly visit and those with missing or broken mobile phones will be noted. Also, all active phone numbers of the participants (as it is not unusual for Ugandans to use more than one SIM card and/or phone) will be recorded to ensure an alternative means of delivering the messages exists, when available. Additionally, participants will be given a handout at the start of the study explaining that they should give the study team a call if they switch phones or phone numbers at any point during the first three months of the study, and that they will be rewarded with 3,000 USh for notifying the study coordinators of such a change.

Outcomes

The study will assess the following outcomes:

Feasibility and Acceptability

The feasibility and acceptability of the INMIND intervention will be assessed by the study retention rate and the attendance rate for scheduled clinic visits, as well as through survey responses collected at the end of the three-month intervention, and following the six-month post-intervention period. These survey measures ask participants about their ability to understand all intervention materials and their perceived value of the intervention. We will also conduct focus groups with a sample of study participants after the post-intervention survey to collect additional information on the study's feasibility and acceptability.

Preliminary Efficacy

Primary Outcome 1: Electronically measured mean medication adherence during intervention
MEMS-data will be collected continuously over the course of the three-month intervention period allowing for mean adherence assessment during the intervention period. Specifically, the number of pill bottle openings detected by the MEMS cap will be used as a measure of each participant's pills taken per day. Mean adherence will then be calculated as the number of pills taken per day during the intervention period, divided by the number of pills prescribed during the intervention for a given participant (i.e., # of actual bottle openings / # of prescribed bottle openings). This mean adherence measure will be capped at 100%, meaning that any pill bottle openings over the participants' number of prescribed daily pills will be ignored. In this way, the mean adherence measure will range from 0 to 100 and will be calculated for each participant on each day of the intervention period. Only one of the daily ART medication doses will be used to calculate the primary mean adherence variable. Both the mean adherence over the three-month intervention and a monthly measure of mean adherence will be calculated and analyzed.

Primary Outcome 2: Electronically measured mean medication adherence post-intervention
Post-intervention, MEMS data will be collected continuously for six months to investigate post-intervention mean ART adherence ('persistence'). The calculation of this outcome is the same as that of *Outcome 1* except for the timeline over which the data will be collected and analyzed.

Primary Outcome 3: Routinization of ART adherence during intervention
In addition to *Outcomes 1 and 2*, a novel measure of routine adherence will be assessed during the intervention period. The novelty of the measure is in that it is explicitly based on the temporal pattern of pill-taking. The measure will be calculated as the fraction of scheduled pills taken within a two-hour window (+/- one hour) around the typical time that participants report completing their existing routine behavior that anchors their pill-taking. This measure provides an objective way for determining the behavioral automaticity of pill-taking, and will be calculated as the mean of all prescribed pills taken around participants' anchor time over the three-month intervention.

Primary Outcome 4: Routinization of ART adherence post-intervention
The fourth outcome will be calculated using the same procedures as *Outcome 3*. However, the data from which the measure will be assessed will be collected during the post-intervention period.

The team will also assess two secondary efficacy measures, as described below:

Secondary Outcome 1: Retention in care

Retention in care is an important metric of treatment adherence. Failure to remain in care is a commonly observed problem for treatment initiators. To assess how well participants will continue to remain in care, Mildmay electronic records will be used to evaluate the number of study participants who fail to observe their regularly scheduled clinic visits. Participants who don't make any clinic visits for six months or more will be considered lost to follow up. The study coordinator will call them using the tracking information collected for the study to inquire about their reason for stopping care at the Mildmay clinic. This outcome will be measured as an indicator of whether the participants are still active clients at the clinic at the end of the nine-month study.

Secondary Outcome 2: Viral Suppression

HIV RNA (viral load) is our final outcome measure. According to the AIDS Clinical Trials Group, virological failure is defined as a confirmed viral load > 200 copies/mL. Below this level, the viral load is considered undetectable. Importantly, this is a reliable biological measure of ART adherence, since strong adherence leads to lower viral load. Given the intervention design, viral load will be an important complementary measure of adherence. The analysis will examine the intervention effects on the likelihood of being virally suppressed at the end of the nine-month study period.

Data Analysis

Statistical Methods and Analyses

Feasibility and acceptability will be analyzed using summary statistics derived directly from our self-reported measures. To estimate preliminary efficacy, statistical analyses comparing group-level differences in the secondary and tertiary outcome measures will be performed. An Analysis of Covariance framework will be used to test for group differences in each secondary and tertiary outcome, controlling for the participant characteristics that are found to differentiate the groups at baseline. For analyses of dichotomous variables, such as viral suppression, a non-parametric McNemar's test and an analogous multiple logistic regression will be used to control for covariates to assess group differences. In addition to static comparisons of group means for each outcome at three-month intervals, the longitudinal nature of the data will be leveraged by using repeated measures and time-series techniques. Specifically, a linear mixed model with repeated observations will be fit using maximum likelihood through 'xtmixed' in the

software package Stata to study group-level temporal dynamics in daily measures of the primary and secondary outcomes.

Sample and Effect-size Estimation

We will recruit a total of 150 participants and will assume a 90% retention rate through the 9-month study period. This is a conservative estimate of attrition, as previous research in the same clinic and with a similar population observed only 6% attrition over 12-month study periods [44,48]. Given the study objectives of establishing acceptability, feasibility, and preliminary effectiveness, the targeted sample size may not have the power to detect many of the effects that would be clinically significant. Nonetheless, effect size calculations associated with 80% power (2-tailed test) with regard to the primary outcomes at month nine have been carried out. A recent study conducted at Mildmay suggested that mean ART adherence rates are ~ 75% (SD = 20) as measured by MEMS caps [44]. Using these parameters as estimates of adherence for the control group, and 10% attrition at month nine, a sample size of 150 will provide sufficient power to detect a 9% difference in mean adherence between the pooled intervention groups and the control group (effect size = .47), and a roughly 11% difference in mean adherence between the two intervention groups. This translates to the study being able to detect medium effect sizes.

Qualitative Analysis

Qualitative analysis will primarily be performed through semi-structured interviews and focus groups with clients, providers, and clinic administrators during the initiation and adaptation phases. The interviews administered during the initiation phase will primarily focus on perceptions of ART pill-taking as an activity of daily life and investigate the range of existing behaviors that could be used as cues (such as eating, daily prayers, or brushing teeth) to refine how INMIND could best support ART adherence routinization. During the adaptation phase, eight focus groups (four among participants in the *Messages* group and four among the participants in the *Incentives* group) will be organized to elicit additional qualitative information on areas of program improvements that may not be captured in the surveys.

All qualitative data will be digitally recorded, translated into English, and uploaded into Dedoose, an analytic software package. Two qualitative researchers will independently read the text and identify all topics covered. A codebook that details the inclusion and exclusion criteria along with typical exemplars for each topic or theme will be developed. Inter-coder reliability (evidenced by

Cronbach's alpha $\alpha \geq 0.70$) will be established until the coders converge on a single, agreed-upon meaning for the thematic area. For each topic, they will identify the range of themes, with attention to those most commonly discussed (i.e., key themes) and least frequently discussed (i.e., outliers). They will produce research reports on specific topics describing the range, central tendency, and distribution of each theme.

Data Management

All data collected during the course of the study (outside of the consent forms, which will include the participants' name and signature) will only have the existing clinic identifiers as the unique participant identifier. All other identifiable information will be stored separately. Data collection and storage hardware (i.e., tablets and computers) will be password protected and physical storage spaces will have a locking mechanism for security. All physical storage spaces will be located at the Mildmay RAND office in Kampala with access granted only to key personnel and the principal investigator (PI). These physical storage spaces will be used to store the consent forms and other physical tracking documentation.

All data collection and on-ground study activities will be carried out by the study team in Uganda. This team will include a team leader, two lead interviewers, and three supporting team members. The design of the data collection instruments and protocols, the quality monitoring of the qualitative and quantitative data, and the data analysis will be carried out by the study team based in the United States (U.S.). Data collected on the ground will be transferred to the US team on a weekly basis through a secure web portal (Kiteworks).

Published material will be free of any personally identifying information. There is no data monitoring committee since the trial was deemed minimal risk. The study team in the U.S. will still perform data monitoring and quality assurance exercises weekly during the nine-month study period.

Handling Missing Data and Attrition

Missing data for some variables will be imputed if a participant remained enrolled in the study. When participants drop out, multiple logistic regression models will be fit to assess whether this dropout is random. If it is not, "nonresponse" weights using logistic regression will be developed to correct for dropout. All analyses will reflect these design effects in the calculation of standard errors and statistical tests of significance.

Results

This pilot study has been funded by the National Institutes of Mental Health in the United States (R34MH122331) and approved by the RAND Human's Subjects Protection Committee (2020-N0632), Mildmay Uganda Research Ethics Committee (0701-2021), as well as the Uganda National Council for Science and Technology (HS128ES). As of February 18, 2022, recruitment was completed. As of August 23, 2023, all the data collection activities were also marked completed; the analyses of the data are ongoing.

Discussion

Expected outcomes

We hypothesize that our two intervention groups will display higher mean medication adherence and higher routinized medication adherence (i.e., pill-taking within +/- one hour of participants' chosen anchor) during the three-month intervention relative to the control group. After more frequently using their anchoring strategy, we then hypothesize that our two intervention groups will better maintain their mean medication adherence and routinized medication adherence over the six months after the intervention is withdrawn. Finally, we hypothesize that our second treatment group that receives both text message reminders and small incentives for using their anchor during the three-month intervention will more strongly maintain their mean medication adherence and routinized medication adherence during the six-month post-intervention period.

Comparison to prior work

INMIND has a strong scientific premise that addresses a critical knowledge gap in the literature around the design of interventions for establishing and maintaining long-term behavior change. A growing literature in the field of psychology targets long-term behavior change [18,43]; however, most of the intervention methods are one-off interventions that do not support participants during the approximately three-month routinization process [17,20,54,55]. Behavioral economics-based interventions have also had limited efficacy in maintaining long-term behavior change. For example, incentives have successfully changed a range of health behaviors by countering present bias [38–41], including improved ART adherence [42], but these interventions typically show only short-term impact that dissipates after the incentives are withdrawn [38,43]. In our own prior studies, we also found that incentives did not have persistent effects, and only participants who showed timely adherence (an indicator that they potentially

anchored pill-taking to an existing routine) maintained high adherence after the incentives were withdrawn [44].

Our combined intervention approach attempts to leverage the successful components of these existing psychology and behavioral economics-based interventions to better maintain ART adherence. If successful, this intervention will help to expand the understanding of the habit formation process and the common psychological barriers to successfully stick to new health behaviors. The study also addresses biological variables such as age and sex appropriately and incorporates them in both the impact analysis and when testing for age and sex differences in behavioral biases and intrinsic motivation. Such analyses will be especially useful in designing a large-scale intervention that can assist all treatment initiators with establishing and maintaining long-term ART adherence.

Limitations

The study is not without limitations. First, the study will sample from one clinic in Uganda, limiting the generalizability of our results. Second, the small sample size limits the team's ability to detect clinically meaningful effect sizes. While this is not the intended aim of this feasibility and acceptability study, the small sample size is still a limitation to the statistical analyses. Third, ART adherence will only be measured over nine months, so future research will be needed to assess ART adherence over longer durations. Fourth, ART adherence will be measured using MEMS caps, which is currently one of the most accurate ways to measure medication adherence, but conscious manipulation of the pill bottle openings by the participants is still a possibility that may lead to an overestimation of the study's adherence outcomes for participants in the Incentives group who may use deception to increase their chances of a prize drawing.

Dissemination and Future Directions

The team will use peer-reviewed publications and conference presentations as the primary means of results dissemination. The findings will be relevant to those interested in the behavioral mechanisms that underly successful long-term ART adherence, and more broadly, the mechanisms underlying long-term behavior change. Additionally, the findings will be utilized in the design of a larger-scale randomized controlled trial that we will use to rigorously assess the effectiveness of the INMIND intervention for establishing long-term ART adherence habits. In addition to future randomized controlled trials, we plan to use the detailed MEMS data on the

timing of daily pill-taking to inform statistical models of the habit formation process, which will guide new intervention designs for promoting ART adherence habits.

Data Availability

De-identified research data will be made available, along with the survey instruments, to interested external researchers through collaborative agreements with the PI and co-investigators, as required by the National Institutes of Health's data sharing policies.

Trial status

The trial was retrospectively registered on Clinicaltrials.gov (registration number: NCT05131165) on 12 November 2021. The study start date was 25 October 2021, and the protocol was last updated on 22 September 2022. The primary completion date was 23 August 2023, and the study completion date is expected to be in August 2025.

List of abbreviations

AIDS: acquired immunodeficiency syndrome
ART: antiretroviral therapy
HIV: human immunodeficiency virus MEMS: medication event monitoring system
SPIRIT: standard protocol items: recommendations for interventional trials

References

1. Palella Jr FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD, Investigators HOS. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. New England Journal of Medicine Mass Medical Soc; 1998;338(13):853–860.

2. Parienti J-J, Ragland K, Lucht F, de la Blanchardière A, Dargère S, Yazdanpanah Y, Dutheil J-J, Perré P, Verdon R, Bangsberg DR. Average adherence to boosted protease inhibitor therapy, rather than the pattern of missed doses, as a predictor of HIV RNA replication. Clinical Infectious Diseases 2010;50(8):1192–1197.

3. Kobin AB, Sheth NU. Levels of adherence required for virologic suppression among newer antiretroviral medications. Annals of Pharmacotherapy 2011;45(3):372–379.

4. Pasternak AO, de Bruin M, Jurriaans S, Bakker M, Berkhout B, Prins JM, Lukashov VV. Modest nonadherence to antiretroviral therapy promotes residual HIV-1 replication in the absence of virological rebound in plasma. The Journal of Infectious Diseases 2012;206(9):1443–1452.

5. AIDSinfo. 2017. UNAIDS: AIDSinfo. Retrieved from http://aidsinfo.unaids.org/# - Google Search [Internet]. [cited 2019 Nov 6]. Available from: https://www.google.com/search?q=AIDSinfo.+2017.+UNAIDS%3A+AIDSinfo.+Retrieved+from+http%3A%2F%2Faidsinfo.unaids.org%2F%23&rlz=1C1GCEA_enUS861US861&oq=AIDSinfo.+2017.+UNAIDS%3A+AIDSinfo.+Retrieved+from+http%3A%2F%2Faidsinfo.unaids.org%2F%23&aqs=chrome..69i57.611j0j4&sourceid=chrome&ie=UTF-8

6. B Nachega J, C Marconi V, U van Zyl G, M Gardner E, Preiser W, Y Hong S, J Mills E, Gross R. HIV treatment adherence, drug resistance, virologic failure: evolving concepts. Infectious Disorders-Drug Targets (Formerly Current Drug Targets-Infectious Disorders) 2011;11(2):167–174.

7. May MT, Gompels M, Delpech V, Porter K, Orkin C, Kegg S, Hay P, Johnson M, Palfreeman A, Gilson R. Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. AIDS (London, England) 2014;28(8):1193.

8. Hardon AP, Akurut D, Comoro C, Ekezie C, Irunde HF, Gerrits T, Kglatwane J, Kinsman J, Kwasa R, Maridadi J. Hunger, waiting time and transport costs: time to confront challenges to ART adherence in Africa. AIDS Care 2007;19(5):658–665.

9. Tuller DM, Bangsberg DR, Senkungu J, Ware NC, Emenyonu N, Weiser SD. Transportation costs impede sustained adherence and access to HAART in a clinic population in southwestern Uganda: a qualitative study. AIDS and Behavior 2010;14(4):778–784.

10. Byakika-Tusiime J, Oyugi JH, Tumwikirize WA, Katabira ET, Mugyenyi PN, Bangsberg DR. Adherence to HIV antiretroviral therapy in HIV+ Ugandan patients purchasing therapy. International Journal of STD & AIDS 2005;16(1):38–41.

11. Gallant JE. Strategies for long-term success in the treatment of HIV infection. JAMA 2000;283(10):1329–1334.

12. Shuter J, Sarlo JA, Stubbs RO, Rode RA, Zingman BS. Sequential antiretroviral adherence measurement using electronic bottle cap monitors in a cohort of HIV-infected adults. Journal of the International Association of Physicians in AIDS Care 2012;11(2):94–97.

13. Ortego C, Huedo-Medina TB, Llorca J, Sevilla L, Santos P, Rodríguez E, Warren MR, Vejo J. Adherence to highly active antiretroviral therapy (HAART): a meta-analysis. AIDS and Behavior 2011;15(7):1381–1396.

14. Gardner EM, McLees MP, Steiner JF, del Rio C, Burman WJ. The spectrum of engagement in HIV care and its relevance to test-and-treat strategies for prevention of HIV infection. Clinical Infectious Diseases 2011;52(6):793–800.

15. Alison Phillips L, Leventhal H, Leventhal EA. Assessing theoretical predictors of long-term medication adherence: Patients' treatment-related beliefs, experiential feedback and habit development. Psychology & Health 2013;28(10):1135–1151.

16. Brooks TL, Leventhal H, Wolf MS, O'Conor R, Morillo J, Martynenko M, Wisnivesky JP, Federman AD. Strategies used by older adults with asthma for adherence to inhaled corticosteroids. Journal of General Internal Medicine 2014;29(11):1506–1512.

17. Wood W, Neal DT. A new look at habits and the habit-goal interface. Psychological review 2007;114(4):843.

18. Lally P, Gardner B. Promoting habit formation. Health Psychology Review 2013;7(sup1):S137–S158.

19. Rothman AJ, Sheeran P, Wood W. Reflective and automatic processes in the initiation and maintenance of dietary change. Annals of Behavioral Medicine Oxford University Press; 2009;38(suppl_1):s4–s17.

20. Redish AD, Jensen S, Johnson A. Addiction as vulnerabilities in the decision process. Behavioral and Brain Sciences 2008;31(4):461–487.

21. Duhigg C. The Power of Habit: Why we do what we do and how to change. Random House; 2013.

22. Pfeffer I, Strobach T. Behavioural automaticity moderates and mediates the relationship of trait self-control and physical activity behaviour. Psychology & Health 2018;33(7):925–940.

23. Gardner B. A review and analysis of the use of 'habit'in understanding, predicting and influencing health-related behaviour. Health psychology review 2015;9(3):277–295.

24. Rothman AJ, Gollwitzer PM, Grant AM, Neal DT, Sheeran P, Wood W. Hale and hearty policies: How psychological science can create and maintain healthy habits. Perspectives on Psychological Science 2015;10(6):701–705.

25. Park DC, Kidder DP. Prospective memory and medication adherence. Prospective memory: Theory and applications 1996;369–390.

26. Prestwich A, Lawton R, Conner M. The use of implementation intentions and the decision balance sheet in promoting exercise behaviour. Psychology and Health Taylor & Francis; 2003;18(6):707–721.

27. Achtziger A, Gollwitzer PM, Sheeran P. Implementation intentions and shielding goal striving from unwanted thoughts and feelings. Personality and Social Psychology Bulletin Sage Publications Sage CA: Los Angeles, CA; 2008;34(3):381–393.

28. Armitage CJ, Arden MA. How useful are the stages of change for targeting interventions? Randomized test of a brief intervention to reduce smoking. Health psychology American Psychological Association; 2008;27(6):789.

29. Sheeran P, Orbell S. Implementation intentions and repeated behaviour: Augmenting the predictive validity of the theory of planned behaviour. European journal of social psychology 1999;29(2–3):349–369.

30. Lally P, Chipperfield A, Wardle J. Healthy habits: efficacy of simple advice on weight control based on a habit-formation model. International journal of obesity 2008;32(4):700.

31. Gardner B, de Bruijn G-J, Lally P. A systematic review and meta-analysis of applications of the self-report habit index to nutrition and physical activity behaviours. Annals of Behavioral Medicine 2011;42(2):174–187.

32. Verplanken B, Faes S. Good intentions, bad habits, and effects of forming implementation intentions on healthy eating. European Journal of Social Psychology 1999;29(5-6):591–604.

33. Beeken RJ, Croker H, Morris S, Leurent B, Omar R, Nazareth I, Wardle J. Study protocol for the 10 Top Tips (10TT) Trial: Randomised controlled trial of habit-based advice for weight control in general practice. BMC Public Health 2012;12(1):667.

34. Enriquez M, McKinsey DS. Strategies to improve HIV treatment adherence in developed countries: clinical management at the individual level. HIV/AIDS (Auckland, NZ) 2011;3:45.

35. Gardner B, Sheals K, Wardle J, McGowan L. Putting habit into practice, and practice into habit: a process evaluation and exploration of the acceptability of a habit-based dietary behaviour change intervention. International Journal of Behavioral Nutrition and Physical Activity 2014;11(1):135.

36. O'Donoghue T, Rabin M. Present bias: Lessons learned and to be learned. American Economic Review 2015;105(5):273–79.

37. Chetty R, Looney A, Kroft K. Salience and taxation: Theory and evidence. American Economic Review 2009;99(4):1145–77.

38. Mantzari E, Vogt F, Shemilt I, Wei Y, Higgins JP, Marteau TM. Personal financial incentives for changing habitual health-related behaviors: A systematic review and meta-analysis. Preventive medicine 2015;75:75–85.

39. Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. Financial incentive–based approaches for weight loss: a randomized trial. Jama 2008;300(22):2631–2637.

40. Volpp KG, Loewenstein G, Troxel AB, Doshi J, Price M, Laskin M, Kimmel SE. A test of financial incentives to improve warfarin adherence. BMC health services research 2008;8(1):272.

41. Charness G, Gneezy U. Incentives to exercise. Econometrica 2009;77(3):909–931.

42. Linnemayr S. Behavioral Economics and HIV: A review of existing studies and potential future research areas. Behavioral Economics and Healthy Behaviors Routledge; 2017. p. 141–156.

43. Wood W, Neal DT. Healthy through habit: Interventions for initiating & maintaining health behavior change. Behavioral Science & Policy 2016;2(1):71–83.

44. Stecher C, Mukasa B, Linnemayr S. Uncovering a behavioral strategy for establishing new habits: Evidence from incentives for medication adherence in Uganda. Journal of Health Economics Elsevier; 2021;77:102443.

45. Dai H, Milkman KL, Riis J. The fresh start effect: Temporal landmarks motivate aspirational behavior. Management Science 2014;60(10):2563–2582.

46. Hodgson I, Plummer ML, Konopka SN, Colvin CJ, Jonas E, Albertini J, Amzel A, Fogg KP. A systematic review of individual and contextual factors affecting ART initiation, adherence, and retention for HIV-infected pregnant and postpartum women. PloS One 2014;9(11):e111421.

47. Buscher A, Hartman C, Kallen MA, Giordano TP. Impact of antiretroviral dosing frequency and pill burden on adherence among newly diagnosed, antiretroviral-naive HIV patients. International Journal of STD & AIDS 2012;23(5):351–355.

48. Linnemayr S, Stecher C, Mukasa B. Behavioral economic incentives to improve adherence to antiretroviral medication. AIDS (London, England) 2017;31(5):719.

49. Cramer J, Vachon L, Desforges C, Sussman NM. Dose frequency and dose interval compliance with multiple antiepileptic medications during a controlled clinical trial. Epilepsia Wiley Online Library; 1995;36(11):1111–1117.

50. Gardner B, Abraham C, Lally P, de Bruijn G-J. Towards parsimony in habit measurement: Testing the convergent and predictive validity of an automaticity subscale of the Self-Report Habit Index. International Journal of Behavioral Nutrition and Physical Activity 2012;9(1):102.

51. Verplanken B, Orbell S. Reflections on past behavior: a self-report index of habit strength. Journal of applied social psychology Wiley Online Library; 2003;33(6):1313–1330.

52. Falk A, Becker A, Dohmen T, Enke B, Huffman D, Sunde U. Global evidence on economic preferences. The Quarterly Journal of Economics Oxford University Press; 2018;133(4):1645–1692.

53. Deci EL, Ryan RM. Intrinsic motivation. The corsini encyclopedia of psychology 2010;1–2.

54. Galla BM, Duckworth AL. More than resisting temptation: Beneficial habits mediate the relationship between self-control and positive life outcomes. Journal of Personality and Social Psychology 2015;109(3):508.

55. Sheeran P. Intention—behavior relations: a conceptual and empirical review. European Review of Social Psychology 2002;12(1):1–36.