

Supplementary Table 1. Sensitivity analysis of the effects of incentives adjusted for prognostic factors, HIV treatment initiates in Tanzania, 2018-2019.

Outcome at six months	N	Group estimate (SE)*			Between-group difference (95% CI), p-value*		
		0 TZS	10,000 TZS	22,500 TZS	10,000 vs. 0 TZS	22,500 vs. 0 TZS	22,500 vs. 10,000
Retained in care and virally suppressed [†]	530	73.0% (0.034)	82.7% (0.029)	86.2% (0.026)	9.8 (1.2, 18.4), 0.026	13.3 (4.8, 21.7), 0.0021	3.5 (-4.3, 11.2), 0.38
Retained in care	530	83.7% (0.027)	88.3% (0.024)	90.9% (0.022)	4.5 (-2.6, 11.6), 0.21	7.1 (0.4, 13.9), 0.039	2.6 (-3.8, 9.0), 0.42
Virally suppressed [‡]	464	86.8% (0.030)	93.8% (0.021)	95.0% (0.018)	6.9 (0.0, 13.9), 0.049	8.1 (1.2, 15.0), 0.021	1.2 (-4.3, 6.6), 0.67
Appointment attendance (%) [§]	530	80.0% (0.017)	87.4% (0.017)	90.6% (0.017)	7.4 (2.8, 12.1), 0.0018	10.6 (5.9, 15.2), <0.0001	3.1 (-1.6, 7.9), 0.19
Total number of visits attended	530	4.29 (0.127)	4.83 (0.131)	5.03 (0.130)	0.54 (0.18, 0.90), 0.0032	0.73 (0.38, 0.11), 0.0001	0.19 (-0.17, 0.56), 0.30

Data are estimates from generalized linear models adjusted for the clinic where randomisation occurred and for prognostic baseline characteristics, including sex, age, and WHO Clinical Stage. TZS=Tanzanian Shillings.

*Viral suppression status was multiply imputed for 33 (6.2% of 530 overall) participants, who remained in care but were missing a valid viral load result.

[†]Primary outcome; the composite proportion of patients who remained in care at six months and had a viral load <1000 copies per mL.

[‡]Among those retained in care (n=464 overall).

[§]The mean patient's proportion of scheduled appointments over six months which were attended within 4 days of the scheduled date.

Supplementary Table 2. Complete case sensitivity analysis excluding participants missing viral suppression status for relevant outcomes, HIV treatment initiates in Tanzania, 2018-2019.

Outcome at six months	N	Group estimate (SE)*			Between-group difference (95% CI), p-value*		
		0 TZS	10,000 TZS	22,500 TZS	10,000 vs. 0 TZS	22,500 vs. 0 TZS	22,500 vs. 10,000
Retained in care and virally suppressed [†]	497	73.7% (0.034)	82.8% (0.029)	86.2% (0.027)	9.1 (0.4, 17.9), 0.041	12.6 (4.2, 21.0), 0.0034	3.4 (-4.3, 11.2), 0.39
Virally suppressed if retained in care [‡]	431	89.6% (0.026)	94.4% (0.019)	95.4% (0.017)	4.9 (-1.5, 11.2), 0.13	5.9 (-0.3, 12.0), 0.061	1.0 (-4.0, 6.0), 0.70

Data are estimates from logistic regression models adjusted for the clinic where randomisation occurred. TZS=Tanzanian Shillings.

*Viral suppression status at six months was missing for 33 (6.2% of 530 overall) participants, who remained in care but were missing a valid viral load result.

[†]Primary outcome; the composite proportion of patients who remained in care at six months and had a viral load <1000 copies per mL. Excludes patients who remained in care but were missing a valid viral load result (n=33).

[‡]Among those retained in care (N=464).

Supplementary Table 3. Heterogeneity by baseline characteristics in effects of incentives (combined groups receiving 10,000 and 22,500 TZS compared to control) on six-month retention in HIV care with viral suppression, Tanzania, 2018-2019.

Subgroup	Group estimate (SE)*		Between-group difference (95% CI), <i>p</i> -value*	<i>p</i> -interaction
	Control	Intervention		
Overall	73.0%(0.034)	84.5%(0.020)	11.5 (3.8, 19.1), 0.0034	
Sex				
Male	68.2%(0.061)	84.3%(0.032)	16.1 (2.7, 29.5), 0.019	ref.
Female	75.9%(0.041)	84.6%(0.025)	8.7 (-0.6, 18.1), 0.066	0.45
Age (years)				
18-24	67.6%(0.097)	85.0%(0.059)	17.4 (-4.9, 39.7), 0.13	ref.
25-34	65.9%(0.059)	83.9%(0.032)	18.0 (4.9, 31.2), 0.0073	0.99
≥35	80.0%(0.044)	84.8%(0.027)	4.9 (-5.4, 15.1), 0.35	0.38
Wealth index				
Low	68.2%(0.063)	87.1%(0.031)	18.9 (5.1, 32.7), 0.0073	ref.
Middle	68.7%(0.058)	82.6%(0.037)	13.9 (0.4, 27.5), 0.044	0.50
High	83.1%(0.053)	83.6%(0.035)	0.5 (-11.9, 12.9), 0.93	0.068
Treatment delay				
0-1 days	64.2%(0.066)	83.1%(0.036)	18.9 (4.0, 33.8), 0.013	ref.
2-7 days	78.9%(0.049)	88.7%(0.030)	9.8 (-1.0, 20.7), 0.076	0.62
>1 week	74.0%(0.062)	80.8%(0.039)	6.8 (-7.4, 21.0), 0.35	0.26

Data are estimates from logistic regression models adjusted for the clinic where randomisation occurred. TZS=Tanzanian Shillings.

*Viral suppression status was multiply imputed for 33 (6.2% of 530 overall) participants, who remained in care but were missing a valid viral load result.

STUDY PROTOCOL

Optimizing the Efficiency and Implementation of Cash Transfers to Improve Adherence to Antiretroviral Therapy

Phase I: Determining the Minimum Effective Cash Transfer Size

Brief Title: Afya II

Sponsor: U.S. National Institutes of Health
R01 MH112432-01A1

Lead Principal Investigator: Sandra McCoy

Local Principal Investigator: Prosper Njau

List of Abbreviations

ART.....Antiretroviral Therapy

PLHIV.....People Living with HIV/AIDS

DSMB.....Data and Safety Monitoring Board

MDH.....Management and Development for Health

TZS..... Tanzanian Shillings

LTFU.....Loss to follow-up

RA.....Research Assistant

CTC.....Care and Treatment Clinic (HIV)

HPONHealth for a Prosperous Nation

Protocol Summary

Title	Optimizing the efficiency and implementation of cash transfers to improve adherence to antiretroviral therapy (Phase 1)
Study objectives	<ol style="list-style-type: none"> 1. Determine the “dose-response” relationship between a cash transfer amount and HIV viral suppression at 6 months 2. Identify the most effective cash transfer size to increase the proportion of PLHIV retained in care and with suppressed viral load (<1000 copies/ml) after 6 months. (This amount will be further evaluated in a cluster randomized trial in Phase 2).
Study design	Randomized controlled trial; participants individually randomized to one of three study arms in a 1:1:1 ratio (standard of care and two active intervention arms).
Study site	The trial will be conducted at four facilities in Shinyanga Region, Tanzania: Shinyanga Regional Hospital, Kahama Hospital, Kambarage Health Center, and Kagogwa Dispensary
Study population	530 eligible participants who meet the following criteria: 1) ≥18 years, 2) living with HIV infection, and 3) initiated antiretroviral therapy ≤1 month prior to enrollment in the study.
Control arm	Participants in the control group will receive the standard HIV primary care services according to Tanzania’s National Guidelines for the Management of HIV and AIDS.
Intervention arms	<p>Two active intervention arms:</p> <ol style="list-style-type: none"> 1. The opportunity to earn 10,000 TZS/month (~\$4.50) for up to 6 months conditional on visit attendance, and 2. The opportunity to earn 22,500 TZS/month (~\$10.00) for up to 6 months conditional on visit attendance <p>In both intervention arms, patients are eligible for the first cash transfer at their first follow-up visit, which is typically 14-30 days after ART initiation. After the first follow-up visit, cash transfers will be delivered a maximum of once monthly, spaced ≥28 days apart, for up to six consecutive months. All transfers will be delivered via an automatic mobile money system linked to a biometric identification system.</p>
Primary endpoint	HIV viral suppression (<1000 copies/mL) at 6 months on ART The primary outcome is the proportion of people living with HIV (PLHIV) retained in HIV primary care and with suppressed HIV

	viral load after 6 months on ART. The primary outcome is expressed as a binary variable, defined as PLHIV who are on ART and with sufficient HIV viral suppression (<1000 copies/ml) versus not on ART or viral failure (≥1000 copies/ml).
Secondary endpoints	<ul style="list-style-type: none"> • Appointment attendance, the proportion of scheduled visits that were completed during the 0-6 month period, • Retention on ART at 6 months, and • The proportion virally suppressed of those with a viral load result.
Sample size	530 participants; the study will have 80% power with a two-sided type I error of 0.05 to detect a dose-response relationship between cash amount and adherence if the proportion with viral suppression in the highest value group (22,500 TZS) is <i>at least</i> 78% and 150 patients per group are available.
Study duration	<p>6 months of follow-up per participant.</p> <p>Participant enrollment and follow-up is expected to be conducted from March 2018 – July 2019</p>

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1. BACKGROUND

Although early initiation of antiretroviral therapy (ART) among people living with HIV/AIDS (PLHIV) has significant clinical benefits and can virtually eliminate onward HIV transmission,[1, 2] these benefits hinge on high levels of ART adherence and retention in care. Most treatment regimens require more than 80-95% adherence to maximize the probability of viral suppression,[3-6] the ultimate goal of HIV treatment.[2, 7] However, in sub-Saharan Africa nearly 25% of PLHIV on treatment have sub-optimal adherence and overall, only 29% of PLHIV are virally suppressed.[8, 9] Disengagement from HIV care is also a pervasive threat to the potential effectiveness of both 'test and start'[1] (ART initiation immediately after HIV diagnosis) and 'treatment as prevention' (TasP)[2] strategies, as only 65% of PLHIV in Africa are retained in care 36 months after treatment initiation.[10] Thus, achievement of UNAIDS' ambitious '90-90-90' strategy, which requires that by 2020, 90% of PLHIV who receive ART will have viral suppression, necessitates new, effective, and *scalable* strategies to bolster ART adherence and retention in care.

Cash transfers are increasingly recognized as an effective strategy to motivate behavior change and improve outcomes along the HIV care continuum. Cash transfers were originally shown to reduce poverty in Latin America, which led to their rapid global expansion, including in Africa.[11, 12] More recently, a proliferation of studies in HIV prevention and care has revealed that under the right circumstances, financial incentives can increase HIV testing, change short-term sexual behavior, and enhance linkage to care.[13-22] Furthermore, our team and others have found that by mitigating the detrimental consequences of poverty and food insecurity on HIV care,[23-25] financial incentives can increase the probability that PLHIV are retained in care, adhere to ART, and have suppressed viral loads.[17, 26] These studies, bolstered by microeconomic and behavioral economic theory,[27] have galvanized program planners to consider cash transfers as part of a comprehensive strategy to increase PLHIV engagement with care. Indeed, systematic reviews have revealed that eight of nine completed studies evaluating the effect of cash incentives (vs. standard of care/no incentive) reported positive effects on adherence or viral suppression in the overall population and/or at least one sub-population.[17, 28-30] However, few of these studies were conducted in sub-Saharan Africa.[28, 31] Thus, the scientific gap is evident and the political climate is opportune to explore whether cash transfers can be incorporated into 'test and start' strategies and brought to scale in sub-Saharan Africa.

We recently completed a study demonstrating that cash transfers improve ART adherence and retention in care among food insecure PLHIV in Tanzania. As part of the PI's Career Development Award (K01MH094246), along with additional funding from NIH (R03MH105327) and PEPFAR, we randomized 800 food insecure PLHIV who recently started ART to the standard of care or 6 months of cash or food transfers, conditional on visit attendance.[26] After 6 months of the intervention, we found that short-term cash transfers were superior to the standard of care on all indicators of adherence and retention, including the medication possession ratio (MPR), a pharmacy-based measure of adherence associated with viral suppression,[32-35] appointment attendance, and loss to follow-up.[31] After 12 months, 6 months *after the intervention ended*, the cash group remained more likely to be in care than the standard of care group and had superior appointment attendance. Furthermore, cash transfers were superior to or equal to food baskets on all outcomes, were cheaper and easier to monitor, and were preferred by patients. Although these data signal short-term efficacy and the potential for longer-term effects, three key questions remain that are applicable to our setting and cash transfer programs for PLHIV in a variety of contexts: 1) could we achieve similar effects with a *smaller* cash transfer, 2) does the short-term intervention have lasting effects on a biological outcome (viral suppression), and 3) is the implementation model suitable for scale? The first of these research questions is the focus of this protocol.

In this study, we will build on these promising preliminary data and refine our cash transfer program. We will fine-tune two critical elements of our previous intervention: 1) cash transfer size, and 2) the implementation model. We selected these two components for the following reasons:

- **Small amounts of cash can have major public health impacts.** We found that a short-term, monthly cash transfer of 22,500 Tanzanian Shillings (TZS, ~\$10) could improve retention and adherence among PLHIV after 6 months.[26] Although this amount is consistent with social protection programs worldwide, including in Tanzania,[36] smaller amounts could potentially achieve similar benefits. For example, small incentives (<\$0.50) *doubled* the probability that people in Malawi received HIV test results,[37] and a study among HIV-infected drug users in India found that \$4 vouchers increased ART initiation by 69% (45% vs. 27%, $p=0.02$).[38] Also in India, a small incentive (<\$2) *doubled* the amount of children who were fully immunized (relative risk (RR): 2.2, 95% CI: 1.5, 2.8).[39] Furthermore, the transfer size is a critical determinant not only of the program's cost, but also its acceptability, feasibility, and potential for scale and sustainability. Thus, we will examine the effect of two cash values on improving adherence to ART and retention in care among PLHIV in Tanzania.
- **To be scalable and sustainable, the delivery model must be simple.** Previously, we enforced a “hard condition” of visit attendance within a narrow window of ± 4 days from the scheduled appointment.[26] Although this was ideal for proof-of-concept, it was resource-intensive to enforce and unlikely to be feasible at scale. Now, we will introduce two innovations to improve scalability. First, we will automate and simplify cash distribution through a mHealth system integrated with mobile money providers. Second, we will relax the strict condition and provide 6 months of cash transfers for visit attendance, even if the visit is late. This *implicit* conditioning via distribution of transfers at the clinic is known as a “soft condition,” which is often sufficient to trigger behavior change without the complexity and expense of strictly enforcing compliance.[40] Relaxing the condition is also reasonable because: 1) most anti-poverty cash transfer programs in Africa are unconditional,[36] 2) conditions don't necessarily improve outcomes,[15, 41] and, 3) hard conditions exclude the worst-off beneficiaries.[12, 36] Thus, these two innovations will increase scalability.

We will conduct a Phase IIb “dose finding” study to refine the intervention and determine whether a *smaller* cash transfer of 6 months duration can improve retention in care and viral suppression. Our intervention is intended to briefly intervene during a window of vulnerability near the time of treatment initiation in order to support the development of good adherence habits and to protect individual and household welfare. We will adapt an established mHealth system that is integrated with mobile money providers to ensure that our cash transfer program could be efficiently implemented in the real world. The study is powered to detect a dose-response trend and will provide rapid feedback, obviating the need for a lengthy effectiveness trial of various cash transfer amounts, which could either be too high (effective and unnecessarily expensive) or too low (inexpensive and ineffective). We will select the best transfer size to move forward for an impact evaluation in the next phase of the project.

1.1 Theoretical Models Guiding Research

The use of incentives for ART treatment adherence is supported by several theories, including Self Determination Theory, which describes engagement in an activity because of an external reward like a cash transfer.[42] In addition, microeconomic theory posits that people acquire more of a less costly good, and less of a more expensive one.[43] In the context of incentives for HIV treatment, incentives *decrease* the cost of adhering to treatment, which subsequently increases demand. Furthermore, individuals often have “present-biased preferences,” placing disproportionate weight on the present while largely ignoring the future.[27, 44] An implication is

that when a behavior, like attending an HIV care visit, has small immediate costs and large delayed benefits, a small immediate incentive may counteract the present costs and tip the balance towards the positive behavior.[17, 27] The use of incentives for behavior change is also supported by behavioral economic theory, which incorporates constructs from psychology to account for the predictable irrationalities, heuristics, and biases of human behavior.[45] For example, “nudges” or short-term, small incentives can change behavior[46, 47] and create new habits[48] – a goal of our short-term intervention.

2. STUDY OBJECTIVES

2.1 Primary objectives and hypothesis

1. Determine the “dose-response” relationship between a cash transfer amount and HIV viral suppression at 6 months.
2. Identify the most effective cash transfer size to increase the proportion of PLHIV retained in care and with suppressed viral load (<1000 copies/ml) after 6 months. (This amount will be further evaluated in a cluster randomized trial in Phase 2).

The primary objective of this study is to describe whether there is a “dose-response” relationship between transfer amount and HIV viral suppression, and the minimum effective cash transfer size to evaluate in the Phase 2 impact evaluation. Using a “dose finding” approach (analogous to the drug development pipeline), we will determine the minimum effective transfer size associated with a $\geq 20\%$ increase in the proportion of PLHIV achieving viral suppression compared to the standard of care after 6 months of follow-up (corresponding to $RR=1.20$ / odds ratio (OR)=1.7 in our study). This effect size was selected to be comparable to other *effective* adherence interventions in sub-Saharan Africa, whose effect sizes range from $OR=1.4$ to $OR=2.07$ (mean $OR=1.75$).[49]

3. METHODOLOGY

3.1. Study setting

The study will be conducted at four HIV primary care clinics in Shinyanga Region, Tanzania: Shinyanga Regional Hospital (4th quarter 2015 HIV case load: 2,870), Kahama District Hospital (4th quarter 2015 HIV case load: 6,497), Kambarage Health Center (4th quarter 2015 HIV case load: 1,304), and Kagongwa Dispensary (4th quarter 2015 HIV case load: 1,753). All HIV care clinics are operated by the Tanzanian government and operate multiple HIV primary care clinics per week.

3.2 Study design

The study is an individually randomized controlled trial. Patients will be randomized within site to one of three study arms in a 1:1:1 ratio using random permuted blocks of 3, 6, and 9.

3.3 Study Arms

There are three study arms: 1) standard of care; 2) 10,000 TZS/month (~\$4.60); and 3) 22,500 TZS/month (~\$10.30). All patients, regardless of arm, will receive standard of care services according to Tanzania’s National Guidelines for the Management of HIV and AIDS.

3.3.1 Intervention arms

Participants in the intervention arms will have the opportunity to receive a monthly cash transfer (10,000 TZS/month (~\$4.60) for those in arm 2, and 22,500 TZS/month (~\$10.30) in arm 3), conditional on visit attendance with the HIV care provider. In general, cash transfers will be given once monthly for *up to* six months, spaced ≥ 28 days apart (consistent with 2017 National Guidelines for monthly or bimonthly visits[50]) and are conditional on visit attendance. This means that the cash transfer is only given when the patient visits the clinic for their routine appointment, regardless of whether the visit is earlier or later than the scheduled appointment. We hypothesize that this simpler condition (compared to the pilot study) that ignores *timeliness* – whether the visit is early or late – will improve intervention feasibility compared to our previous study while maintaining effectiveness because: 1) it requires fewer person-hours to enforce, 2) cash transfers can only be disseminated when a visit occurs, and 3) there is an implicit ‘penalty’ for coming late to the visit because it results in a delay in receiving the transfer. Participants can receive up to 6 consecutive transfers, which was selected because lengthy periods of cash transfers are unlikely to be sustainable. Transfer amounts are exclusive of transaction fees (<\$1), which will also be included in the transfer. Thus, the intended amount is transferred to the patient upon withdrawal. All transfers will be delivered via an automatic mobile money system linked to a biometric identification system.

Visit Scheduling After ART Initiation and Cash Transfer Distribution

Under the 2017 National Guidelines for the Management of HIV and AIDS, patients starting ART are scheduled for a follow-up visit between 14 and 30 days after ART initiation. After that, patients are monitored at monthly clinic visits until the first viral load test is recommended 6 months after ART initiation. At that time, “stable” patients (those who have attained viral suppression) will be given two-month refill appointments, and they do not necessarily need to come in person to the pharmacy to obtain a refill (they can send a substitute). At 12 months, stable patients will have a clinical appointment to assess their progress, but they can still receive care if they are symptomatic. However, at 6 months, unstable patients (those without viral suppression) will continue monthly visits, with enhanced adherence interventions or change of regimen, depending on clinical, immunological, and virological criteria, until they are determined to have stabilized. Thus, the ~6-month visit with the viral load test takes on special significance under this new model of care, and the intervention is intended to support patients during the vulnerable first few months of treatment. Our goal is to support Tanzania’s new differentiated care model by ensuring that the intervention strengthens good habits in the early months of ART.

The variation in visit scheduling does present some complication for distribution of cash transfers and obtaining specimens for viral load quantification. Some patients will follow a simple monthly schedule of visits at 1, 2, 3, 4, 5, and 6 months post-ART initiation. However, a subset of patients newly starting ART (especially those on NVP-containing regimens) will have their first appointment scheduled at 14 days post ART initiation (month 0.5) and will have subsequent monthly visits at 1.5, 2.5, 3.5, 4.5, 5.5, and 6.5 months after initiation. The 6 month viral load test is required at 6 months; thus, these patients are instructed to visit the clinic at 6 months for a viral load test only; this visit does not include a clinical evaluation nor pharmacy pick-up.

Consequently, we have determined the following rules for cash transfer distribution. The first cash transfer will be delivered after completion of the first follow-up visit, which occurs between 14-30 days after ART initiation. Subsequently, cash transfers must be spaced ≥ 28 days apart, consistent with National Guidelines for monthly or bimonthly visits[50]. Participants may receive

up to six consecutive months of transfers. The viral load test will be conducted on the first visit occurring in the 6th month of ART monitoring (e.g., at 5.5 months or 6 months).

3.3.2 Cash transfer distribution

The cash transfer will be distributed through the Rasello mHealth system, adapted for this study. At enrollment, the participant's name, phone number, mobile money account information (if applicable), enrollment date, and cash transfer size (in one of the cash transfer groups) will be registered in the Rasello system by study personnel on a tablet computer. In addition, the participant will register several fingerprints associated with his/her profile. (A short survey will also be conducted, described below).

At the completion of the patient visit, the participant will visit the facility pharmacy to pick up his/her ART. The dispenser at the pharmacy will take the participant's fingerprints using a fingerprint scanner and will record the number of pills dispensed in the system. This procedure will be followed regardless of study group. In the case of cash transfer recipients, the Rasello system will automatically verify the participant's fingerprints and will automatically schedule the mobile money transfer to that participant. Rasello's system is integrated with all major mobile money service providers in Tanzania (i.e., M-Pesa, Airtel Money, TigoPesa). Mobile money is a secure and convenient way for financial transactions,[51] as mobile money kiosks are ubiquitous in Shinyanga and mobile phone ownership in Tanzania is high and approaching levels in the U.S. (73% in 2014 and rapidly increasing[52]).

If a participant does not have a mobile money account or phone: 1) s/he can sign up and return to the clinic on a different day to enroll, 2) s/he may ask a trusted friend or relative to receive the transfer, or 3) s/he can opt to obtain cash directly.

3.4 Trial Endpoints

The primary endpoint is viral suppression at 6 months.

- Viral suppression at 6 months is defined the proportion of people living with HIV (PLHIV) retained in HIV primary care and with suppressed HIV viral load after 6 months on ART. The primary outcome is expressed as a binary variable, defined as PLHIV who are on ART and with sufficient HIV viral suppression (<1000 copies/ml, WHO's threshold for virologic failure in LMICs[55]) versus not on ART or viral failure (≥1000 copies/ml). This outcome definition reflects global "treatment as prevention" strategies including the UNAIDS 90-90-90 targets, which aim for at least 90% of PLHIV to be on ART and 90% of these virally suppressed. (Long-term viral suppression without ART is rare, likely well under 0.5%.)
- Patients considered not on ART include those who died, stopped ART and/or disengaged from care, or have not apparently received ARVs for ≥28 days since their last missed pharmacy pick-up [i.e., are lost to follow-up (LTFU)] following PEPFAR Monitoring, Evaluation, and Reporting Indicator Reference Guide Version 2.3 for current ART.

The secondary endpoints are:

- Appointment attendance, the proportion of scheduled visits that were completed during the 0-6 month period;
- Retention on ART at 6 months; and
- The proportion virally suppressed (<1000 copies/ml) of those PLHIV with a viral load result.

3.5 Sample Size

The sample size was determined for objective #1: Determine the “dose-response” relationship between a cash transfer amount and HIV viral suppression at 6 months. We computed the sample size necessary for a trend test based on the observed 6-month mean medication possession ratio $\geq 95\%$ (MPR $\geq 95\%$) in the pilot study, given MPR’s correlation with viral suppression.[32-35] MPR is the proportion of days in a specified interval that an individual is in possession of ≥ 1 ART dose.[32] MPR is computed from pharmacy dispensing records and achievement of $\geq 95\%$ MPR is associated with short-term virologic outcomes.[32, 35]

Note that in dose-response studies, detecting a statistically significant difference in pairwise comparisons is not necessary if a statistically significant trend (upward slope) can be established.[56] Stated simply, the dose-response curve is used to estimate the likely effectiveness of any dose. Once the optimal dose for the desired goal is selected, an additional study is needed to demonstrate effectiveness of that dose versus comparison (to be examined in Phase 2).

If we assume that 63% of patients will achieve suppressed viral load at 6 months in the standard of care group (0 TZS, based on the prior study[31]), the study will have 80% power with a two-sided type I error of 0.05 to detect a dose-response relationship between cash amount and adherence if the proportion with viral suppression in the highest value group (22,500 TZS) is *at least* 78% and 150 patients per group are available. With three arms and adjusting for 15% LTFU, we require 530 patients for the study, which is well within expectations for the hospital caseloads and 6-month period of recruitment.

3.6 Risk of attrition

As retention in care is one of the outcomes of this study, no additional retention activities are implemented other than the routine procedures already in place and led by clinical staff. Currently, patients in Shinyanga who meet the criteria for loss to follow-up are tracked in the community by a system of home-base care providers; we will leverage this system for finding patients with missed visits and potentially to obtain missing plasma specimens for viral load quantification.

The proportion of patients that are lost to follow up, defined as defined as ≥ 3 months since the last scheduled visit, will be measured as an indicator of retention in care. In the pilot study at three of the same health clinics in 2014-2016, LTFU was 2.6% overall at 6 months, 10.9% in the standard of care arm, and 0.9% in the cash transfer arm.[31] Nevertheless, for the viral suppression outcomes, we have estimated for the power calculations that 15% of patients will be LTFU (overall) in the 6 month follow-up period.

3.7 Procedures

3.7.1 Eligibility, screening and recruitment

We will recruit participants from four HIV primary care clinics in Shinyanga (Kahama District Hospital, Shinyanga Regional Hospital, Kambarage Health Center, and Kagongwa Dispensary). These individuals will be selected from the group of adult men and women who are already attending HIV primary care clinics where the study will take place, or who are newly initiating care. Eligible participants are: 1) ≥ 18 years, 2) PLHIV, and 3) initiated antiretroviral therapy ≤ 1 month prior. Although few patients are expected to have viral load results at baseline through

routine government services,[57] those who are virally suppressed are indeed eligible if they meet the other eligibility criteria.

Participants will be recruited by research assistants affiliated with Health for a Prosperous Nation (HPON), a Tanzanian NGO based in Dar es Salaam with an office at the Shinyanga Regional Hospital. Research assistants (RAs) will be supervised by the Project Director, who is also an employee of HPON hired by the research team, and will be trained by Dr. McCoy and Dr. Njau on research procedures with a particular emphasis on protecting participant confidentiality. Most research activities (except for specimen collection, which will be conducted by trained nurses/laboratorians) will be undertaken directly by the study team; healthcare providers will therefore not be compensated for enrolling participants or for the number of enrolled participants. The healthcare facility will, however, receive a small stipend to compensate for the additional specimen collection activities required as part of the study.

To identify eligible participants, RAs will review the weekly appointment list for the HIV primary care clinic on each preceding Friday. This list is routinely maintained by the clinic and includes the patient's age, time on ART, and appointment day. All patients on the list are living with HIV infection. Patients who meet the inclusion criteria described above will be approached at the time of their regularly scheduled HIV care visit, (as listed on the weekly appointment list) by a RA who is fluent in Kiswahili and trained in study procedures. The RA will discretely ask the potential participant if s/he is interested in learning more about the study and if interested, will tell him/her about the study goals, procedures, and requirements. If s/he is willing to participate, the RA will complete the formal written informed consent process where the potential risks and benefits are clearly explained. The RA will then answer any questions and verbally confirm that the participant understands the informed consent document by administering a brief set of comprehension questions.

In this study, health facility staff cannot unduly influence patients to participate because they will not be directly involved in the recruitment of study subjects. Furthermore, at the time of enrollment, nurses/physicians will not know which subjects are eligible or ineligible or which subjects consent to enroll in the study. Participants can de-enroll from the study anytime they wish and will be told they can do so during the informed consent process.

3.7.2 Written informed consent

Eligible participants will be asked to provide written informed consent for their inclusion in the study. As part of the informed consent process, the RA will explain the study and its goals and review all of the elements of informed consent with the individual. Research assistants are fluent in Kiswahili and will be thoroughly trained in study procedures, including how to present and describe the study using locally understood and meaningful descriptions. During the informed consent process, potential participants will be assured that refusing participation will not impact them or their receipt of health care at the facility and that participation is entirely voluntary. After the RAs thoroughly explain the consent form and answer any questions related to the study or participation, participants will be quizzed on key points regarding participation to ensure that they have adequately understood the information. (Note: Consent forms will be read aloud to potential participants unless individuals insist that they are comfortable reading the form themselves). The comprehension questions will include:

- How will your study group be determined? (Answer: by chance / randomly)
- When do participants receive transfers? (Answer: when they attend a scheduled visit)
- For how many months participants earn transfers? (Answer: up to 6 months)

Potential participants who provide written informed consent and successfully answer the comprehension questions will be invited to enroll in the study.

Incomplete Disclosure of Study Groups

We will use incomplete disclosure in this study to mask study participants to the intervention groups. In the informed consent process, we will not tell participants that there are two cash arms plus a standard of care arm. Instead, we will tell them there that the study has one cash group and one comparison group, and we will not reveal that there are two cash amounts being evaluated in the research study. We will also not reveal the cash amount until after randomization.

This strategy is critical to ensure the validity of the study. Data from the incentive literature suggest that non-linear spillover effects of incentives could occur such that if participants in the smaller cash arm (10,000 TSH) know that they could have received 22,500 TSH, they may actually be de-motivated to remain in care or in the study – precluding an accurate evaluation of our research question. (This problem is counterintuitively less of an issue for people who do not receive incentives at all). For this reason, we will imply in the consent process that there is only one cash arm, and we will reveal the amount they could earn (if assigned to a cash group) *after* we have randomized the patient to the study group, immediately after consent.

Incomplete disclosure in this study is justified for the following reasons:

1. The study does not involve any more than minimal risk to the subjects. Study procedures are not affected by the incomplete disclosure of the study's two cash transfer arms. In addition, participants will learn their cash transfer amount (if applicable) immediately after randomization.
2. The use of incomplete disclosure about the study groups will ensure that the study has a high level of internal validity and is therefore able to answer the research question under consideration. Furthermore, there is no reasonable alternative method that would be equally effective at masking study participants to the various cash transfer arms.
3. The research is not expected to cause physical pain or severe emotional distress.
4. The research meets the criteria for a waiver of one or more elements of informed consent as set forth in federal regulations at 45 CFR 46.116(d).

Note that these procedures have been conditionally approved by the UC Berkeley IRB; a debriefing session with participants was deemed unnecessary by the IRB and removed from the protocol.

Individuals who would like to participate can sign the informed consent form. Participants who would like to participate but feel uncomfortable signing the consent form will be asked to put a thumbprint (instead of a signature) at the bottom of the document. In addition, RAs will sign the two copies of the consent form, noting that they have obtained written informed consent. A copy of the signed informed consent form will be provided to participants who wish to have a copy.

As for patients who do not provide written informed consent (or a thumbprint/mark), no identifiable information will be obtained as part of the recruitment process. However, we will maintain aggregate data about the numbers of patients who were approached and provided consent to be compliant with international reporting standards for randomized trials (i.e., total number of participants assessed for eligibility, percent that were eligible, reasons for exclusion).

3.7.3 Data collection

If a patient is eligible and provides written informed consent (or a thumbprint/mark), they will be assigned a unique study ID and will complete the in-person baseline survey. Data will also be abstracted from medical and pharmacy records and the mhealth system by the research team at 3-month intervals during the study period. Blood specimens will be collected at 6 months.

3.7.3.1 Survey data

A research assistant will conduct a 30-45 minute survey at baseline and endline (6 months) with each participant in a quiet and private area at the clinic. All surveys will be conducted in Kiswahili using a tablet computer loaded with the Rasello system (which will potentially be integrated with Qualtrics Offline surveys). We have outlined the recruitment and consent procedures above in detail including study comprehension questions. Participants will be reminded that participation is entirely voluntary and that they can refuse to answer any question or leave the survey at any time and that such action will not impact them or their receipt of health services in any way. The baseline survey will measure sociodemographic characteristics and other salient personal characteristics (e.g., intrinsic motivation for adherence, participation in the labor force). The endline survey will measure adverse events, functional limitation and participation in the labor force, and questions about the cash transfer, including whether they knew of others in the study and whether they knew his/her study arm (to assess spillovers).

Participants will be offered a small token of appreciation for their time taking the survey (5,000 TSH, approximately equal to US\$2.20). We have discussed this amount with local stakeholders to ensure that the compensation is consistent with local standards and reduces the potential for coercion. Randomization to the three groups will be done on the tablet computer at the end of the survey.

3.7.3.2 Patient medical records and mhealth system

In addition to the survey, at baseline and every 3 months thereafter we will retrospectively abstract data from patient health records. In many facilities in Shinyanga, there is a MoHCGEC-supported electronic database that is updated daily. In those facilities, we will download data about appointment attendance (scheduled and attended), viral suppression and CD4 count (when available), other clinical markers, pharmacy dispensing, and follow-up status (e.g., lost to follow-up, died). In facilities without the database, we will abstract data from paper records into portable tablet computers.

As mentioned above, the adapted Rasello mhealth system will be used to deliver the cash transfer. Data on intervention uptake can be obtained from this system. In addition, participants who attend a visit will have this information captured in the system, in addition to the next appointment date, thereby allowing the system to capture nearly 'real-time' electronic data about visit attendance.

3.7.3.3 Viral Load Quantification

Viral load quantification will be conducted at 6 months, consistent with WHO and Tanzanian guidelines for monitoring HIV infection. The specimen will be drawn during first visit occurring during the 6th month of ART monitoring (either at 5.5 or 6 months, depending on the patient schedule pattern). Specimens will be identified with the unique 14-digit HIV patient ID assigned to all HIV patients in Tanzania as well as the unique study ID. Each sample will be accompanied by a completed national standard viral load sample collection form. Whole blood samples (4ml) will be transported to the hospital laboratory within 6 hours, checked for quality, assigned barcodes, and entered into the MDH laboratory database. Samples will be centrifuged to

retrieve plasma and stored at -20°; samples will be transported biweekly by EMS to the Management and Development for Health (MDH) lab in Dar es Salaam for testing. Samples will be transported biweekly by EMS courier. We will use the Cobas AmpliPrep (CAP)/Cobas TaqMan (CTM) 96 HIV-1 assay (Roche Molecular Systems, Branchburg, NJ) and Cobus 4800 for HIV viral load quantification. HIV viral load data of each patient will be available in the laboratory database within two days of sample arrival at the laboratory.

4. EVALUATION

4.1. Evaluation Objectives

The evaluation of this randomized controlled trial aims to answer the following questions:

- a) Is a smaller cash transfer size as effective as previously used larger amounts?
- b) What is the minimum effective cash transfer amount?
- c) Is there a dose-response relationship between cash size and viral suppression?
- d) Given a dose-response relationship, is the gain in viral suppression worth the increase in cash size?

4.2 Analysis of primary outcomes

Following procedures for a dose-response study,[58] we will model the relationship between the ordinal exposure (cash amount) and the binary outcome (viral suppression).

The first part of the primary analysis will evaluate the dose-response relationship between cash transfer size and HIV viral suppression at 6 months on ART (Hypothesis 1). We will construct the following logistic regression model: $\text{logit}(p) = a + b \cdot x$, where p is the binomial proportion on ART and virally suppressed (<1000 copies/ml) and x is the ordinal cash amount (coded as 0, 10000, or 22,500 TZS). The null hypothesis is $H_0: p_1=p_2=p_3$ (no trend, such that the proportion is the same for all levels) against the two-sided alternative hypothesis $H_a: p_1 < p_2 < p_3$ or $p_1 > p_2 > p_3$. We will conduct this test using the logistic regression model above, where these hypotheses are equivalent to $H_0: b = 0$ versus $H_a: b \neq 0$, using $\alpha=0.05$.

For the primary analysis, the model will include enrollment site (4 clinics) to account for stratified randomization; the model will not include any additional covariates for the primary analysis. As a secondary analysis, we will additionally adjust for prognostic factors (age, sex, WHO clinical stage at baseline). We will also test for baseline imbalance in sociodemographic and clinical characteristics (e.g., age, sex, language, education, marital status, occupation, work status, head of household, household size, food security, distance to clinic, asset index, days since starting ART, weight, WHO clinical stage) using chi-square and one-way analysis of variance tests at $\alpha = 0.05$; any imbalanced characteristics will also be included in the model for the secondary analysis. We will estimate missing values of included covariates using multiple imputation if $\geq 5\%$ of participants are missing at least one of these covariate values.

4.2.1 Selection of the Best Cash Transfer Size

The selected cash transfer size will be the estimated *minimum* amount necessary to achieve a 20% increase in the proportion of patients achieving viral suppression at 6 months. If a statistically significant dose-response relationship exists as evaluated above, we will use the same logistic regression model to select the minimum effective transfer size, even if it is not one of the amounts tested. The point estimate on the dose-response curve corresponding to a 20% increase relative to the standard of care will be identified and considered for use in Phase II of

the study (a cluster-randomized RCT). This approach has the potential to identify a minimum effective transfer size other than one of the exact amounts studied. However, other factors will also be considered in the final decision, such as qualitative information about local denominations of currency, government and other stakeholder input, and budget considerations.

If the dose-response relationship does not exist as evaluated above OR if neither amount achieves the 20% effect size threshold, we will instead proceed with a direct comparison of the intervention arms. We will construct a generalized linear model using the binomial distribution and identity link (whereby coefficients are expressed as risk differences), where the outcome is the proportion virally suppressed at 6 months on ART and the exposure is categorical transfer size (entered as indicator variables for 10000 and 22500 TZS groups).

Using this model, we will assess whether there is a significant difference in viral suppression between the 10000 and 22500 TZS groups. We will evaluate the difference in coefficients for the two groups (e.g., using the `lincom` command in Stata) at $\alpha=0.05$. We will then use the following decision rule:

- 1) If there is no difference between the two amounts, we will proceed with 10000 TZS for Phase II of the study (to minimize costs and maximize beneficiaries).
- 2) If 10000 TZS is more effective than 22500 TZS, we will proceed with 10000 TZS for Phase II of the study.
- 3) If 22500 TZS is more effective than 10000 TZS, but per above it does not reach the 20% criterion, we will apply a cost-effectiveness criterion. We will express the percentage increase in viral suppression achieved in the 22,500 TZS arm in terms of disability-adjusted life-years (DALYs).[63, 64] This result will be used to determine whether the additional benefits associated with the larger transfer are worthwhile in monetary terms using WHO cost-effectiveness thresholds.[65] We will then proceed with the most cost-effective value, alongside the other qualitative considerations mentioned above.

4.2.2 Protocol fidelity

A number of measures will be put in place to track and monitor the fidelity of intervention implementation. If there are indications that intervention implementation may differ from the study protocol, we will account for the off-protocol deviations. We will create indicators to identify the individuals affected and assess to what extent these affected cases differ from the rest of the study arm sample. We will also compare the sensitivity of the results of the protocol deviations.

4.3. Economic Evaluation

Using a micro-costing approach, we will track the costs of personnel, the mHealth system, cash transfers, and transaction costs. We will estimate unit costs and quantities of inputs, differentiating fixed and variable costs at the clinic and at higher levels of the health system. We will also assess how to reduce costs, if necessary, and use resulting fixed and variable cost estimates to project costs at scale.

5. MONITORING AND QUALITY ASSURANCE

5.1 Real-time supervision of surveyors

Data will be reviewed for quality and completeness by team supervisors during survey administration. A field supervisor is responsible for accompanying each surveyor in his/her team

during at least one hour in the field per day to ensure data is being collected in accordance with the protocol and to trouble-shoot challenges in real-time. At certain time intervals, the field supervisor will collect all the tablets and notebooks of the surveyors under his/her supervision and verify the data collected before passing the tablets over to the tablet supervisors. The tablet supervisors will verify the data in each tablet, particularly questions concerning key variables, to ensure their completeness and internal consistency. The tablet supervisors will then give the tablets back to the field supervisors, who distribute them among the surveyors under their supervision to continue data collection. Surveyors will be redeployed to correct and/or complete surveys that are incomplete.

5.2 Real-time monitoring of process data

The Rasello mhealth system captures information on scheduled visits, attended visits and cash transfers. Hence, the system allows us to log in, view data, keep track of and monitor activities and outputs daily. Specimens collected and transported to the local laboratory will be entered into the laboratory database along with unique patient IDs, specimen barcodes and dates of specimen collection. This process will be monitored using the laboratory database.

5.3 External monitoring

A formal analysis plan will be reviewed and approved by a Data and Safety Monitoring Board (DSMB) appointed for the trial. The DSMB will review the results of an interim analysis of study primary outcome and monitor the quality of project implementation.

6. DATA MANAGEMENT

Data will be stored in and accessed from the mhealth system (cash transfer, scheduled visit, attended visits and dates), and a password-protected cloud-based storage folder (data abstracted from patient records, i.e. viral suppression, CD4 count, pharmacy dispensing, and other clinical markers). Data on specimens and collected blood samples will be accessed from the MDH laboratory database.

7. STUDY TIMELINE

The trial will begin in March 2018. In the months leading up to the intervention launch, ethical review board applications and mhealth system development will take place. We plan to implement and conclude this study within 2 years.

Project timeline (Phase 1)	2017		2018												2019						
Color Key - Blue: UCB, Green: Rasello, Purple: HPON, Teal: MDH	N	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J
1. Preparatory activities																					
1. Ethical review board applications, subcontract initiation	Blue	Blue	Blue																		
2. mHealth system development		Green	Green	Green																	
3. Development of survey interface			Green	Green																	
4. SOPs and protocol development	Blue	Blue	Blue	Blue																	
5. Hiring of staff (HPON)		Purple	Purple																		
6. Staff training (HPON)			Purple	Purple																	
7. Establishment of DSMB		Blue	Blue																		
8. Training of laboratory personnel (Shinyanga, MDH)								Teal	Teal												
2. Participant Enrollment and Follow-up																					
Enrollment, Randomization, Baseline Survey					Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple							
Data abstraction from patient records								Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple	Purple
Viral load quantification										Teal	Teal	Teal	Teal	Teal	Teal	Teal	Teal	Teal	Teal	Teal	Teal
3. Intervention Delivery																					
Cash transfer distribution and follow-up						Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green
4. Endline Data Collection																					
Review data in mhealth system								Blue				Blue			Blue	Blue	Blue	Blue	Blue	Blue	Blue
Data abstraction from patient records								Purple				Purple			Purple	Purple	Purple	Purple	Purple	Purple	Purple
6. Data analysis & Dissemination of Results																					
Analysis of primary outcomes and selection of optimal cash transfer size																					Blue
Dissemination of Results																					Blue

8. SAFETY AND ETHICAL ASPECTS OF THE PROJECT

We will obtain clearance from the Committee for Protection of Human Subjects at UC Berkeley and the National Institute of Medical Research in Tanzania. As the study is evaluating an intervention that provides cash to PLHIV receiving the standard of care services, there is minimal risk involved in study participation. The physical risks of this study are minimal. We will conduct viral load testing, which requires venipuncture. Drawing blood may cause temporary discomfort from the needle stick, bruising, or very rarely, infection. However, in this study participants will already have their blood drawn for other routine tests as part of their HIV care (i.e., routine viral load testing every 6 months[50]) and thus they will not require any additional blood draws. The physical risks associated with blood draw will be minimized by having trained health facility professionals obtain the blood samples.

The non-physical risks associated with the study include psychological distress or breach of confidentiality. In the surveys we conduct, participants may experience some discomfort or anxiety when sharing information about sensitive topics such as economic insecurity or whether they liked the cash transfer program. In order to minimize these risks, participants will be told that they can skip any questions that make them uncomfortable or they do not wish to answer. However, it is very unlikely that answering survey questions about these issues will result in long-term or severe distress. In addition, loss of confidentiality resulting from personal information inadvertently being shared with outside individuals may have repercussions, including anger from family members or friends. To ensure confidentiality of information, all staff with access to the data or who interact with participants will sign confidentiality agreements and will be informed of their responsibility to maintain confidentiality. All participants will be informed that surveys are confidential (as stated in the informed consent process) prior to their agreement to participate.

8.1 Confidentiality of study participants

We will adhere to strict measures to ensure the confidentiality of the data after the interviews are complete (as outlined in our ethical review board applications to the National Institute of Medical Research (NIMR, Tanzania) and the Center for the Protection of Human Subjects (University of California, Berkeley)). In addition, we have established a research site and have hired and trained study personnel in Shinyanga who adhere to well-established data collection and management systems. A key policy of our research group is that the fewer individuals handling sensitive information, the greater the protection. Thus, project files and databases will only be available to research personnel through the authorization of the PI (Dr. McCoy). Access to any of the data will be limited to the PI, relevant mentors and advisors, and other key personnel, and require a password at all times. All staff with access to the data will sign confidentiality agreements to maintain confidentiality even after they have left the study or the study has ended. The team has a standard operating procedure in place to conduct quality control spot checks and ensure the privacy and confidentiality of study participants, data collection forms, and electronic data. Staff will be trained on the policies and procedures for data management and transmission and will receive instructions on how to report any violations of those policies and procedures. All staff will be appropriately trained in the handling of sensitive study data through their employment training and annual completion of training in the ethical conduct of research (UC Berkeley staff and students). The PI will review all procedures for protecting confidentiality with study staff on a bi-monthly basis, including storing the data and questionnaires in secure databases and locked file cabinets in locked offices, password protection, and procedures for transferring study data to the secure password-protected cloud-based folder. All data collected in the study will be anonymized prior to sharing with the research team. This de-identified data cannot be linked back to individual participants. No subjects will be identified in any report or publication of the study or its results.

9. TRIAL SPONSORS AND MANAGEMENT

The trial is sponsored by the National Institute of Health. The DSMB will oversee the safety of the trial to ensure that the trial is conducted to quality and safety standards.

10. ROLES OF THE INVESTIGATORS AND COLLABORATORS

The UC Berkeley team (McCoy, Dow, Padian and Jewell) will be responsible for conducting the trial and analyzing the trial results. As part of the UCB team, Stefano Bertozzi will serve as a senior advisor.

The HPON team (Njau) will support field operations and provide supervision. Senior advisors will consult on scientific aspects of the study (Mfaume, Kapologwe, Ramadhani, Kamagenge).

The Rasello team (Mwenda) will be responsible for developing and implementing the mhealth system including the biometric system for dissemination of cash transfers through mobile banking and development of the survey interface.

The Management and Development for Health (MDH) team (Ulenga) will train local laboratory staff, monitor the collection of blood specimens, and oversee HIV viral load quantification.

11. STAKEHOLDER ENGAGEMENT AND DISSEMINATION PLAN

A strong research collaboration has already been established between the Shinyanga Regional Medical Office, HPON, and UC Berkeley. This link will facilitate the incorporation of the trial findings into national health policy and HIV care practices. In addition, there will be an inception meeting with the local medical officers, health facility staff and CTC in-charges to discuss the project and solicit their feedback on the protocol.

Results from the trial will be presented at conferences and in peer-reviewed journals and will be discussed with the study clinics at the end of the trial.

12. LIMITATIONS

We will randomize individuals within facilities, so there is a small risk that people will become less motivated if they learn others are receiving a larger transfer. In the unlikely event that enrollment is slower than expected, we will: 1) determine whether there is a problem with the inclusion criteria, recruitment process or intervention which we will immediately rectify; 2) reassess screening and recruitment procedures to ensure that eligible men and women are not inadvertently missed at the clinic; and 3) explore the feasibility of expanding to additional sites or regions. Lastly, if SMS messages for PLHIV become the standard of care in Shinyanga during the study period, we will include this element in the comparison group.

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Author(s)

Carolyn Fahey (UC Berkeley) - cfahey@berkeley.edu
Nicholas Jewell (UC Berkeley) - jewell@berkeley.edu
Sandra McCoy (UC Berkeley) - smccoy@berkeley.edu

1) Have any data been collected for this study already?

It's complicated. We have already collected some data but explain in Question 8 why readers may consider this a valid pre-registration nevertheless.

2) What's the main question being asked or hypothesis being tested in this study?

Question 1. Is there a "dose-response" relationship between the amount of a monthly conditional cash transfer and the proportion of people living with HIV infection who achieve HIV viral suppression (<1000 copies/ml) after the first 6 months of antiretroviral therapy (ART)? The three amounts being studied are monthly transfers of: 0, 10000, and 22500 Tanzanian Shillings (TZS). The null hypothesis is $H_0: p_1=p_2=p_3$ (no trend, such that the proportion is the same for all levels) against the two-sided alternative hypothesis $H_a: p_1 < p_2 < p_3$ or $p_1 > p_2 > p_3$.

Question 2. What is the minimum effective cash transfer size associated with a $\geq 20\%$ increase in the proportion of patients with HIV infection who are retained in care and with HIV viral suppression (<1000 copies/ml) compared to the standard of care at 6 months?

3) Describe the key dependent variable(s) specifying how they will be measured.

i. HIV viral suppression (<1000 copies/mL) at 6 months on ART

The primary outcome is the proportion of people living with HIV (PLHIV) retained in HIV primary care and with suppressed HIV viral load after 6 months on ART. The primary outcome is expressed as a binary variable, defined as PLHIV who are on ART and with sufficient HIV viral suppression (<1000 copies/ml) versus not on ART or viral failure (≥ 1000 copies/ml). This outcome definition reflects global "treatment as prevention" strategies including the UNAIDS 90-90-90 targets, which aim for at least 90% of PLHIV to be on ART and 90% of these virally suppressed. (Evidence demonstrates that long-term viral suppression without ART is rare, likely well under 0.5%.)

Patients considered not on ART include those who died, stopped ART and/or disengaged from care, or have not apparently received ARVs for ≥ 28 days since their last missed pharmacy pick-up [i.e., are lost to follow-up (LTFU) from clinic-based care] following PEPFAR Monitoring, Evaluation, and Reporting Indicator Reference Guide Version 2.3 for current ART. Treatment status at 6 months will be determined after exhaustive tracing attempts (≥ 3 attempts using at least two tracing methods, including, for example, phone calls, home visits from a community health worker, or triangulation with other health facilities). If medical records or tracking results indicate that a participant transferred to another health facility, the appointment records from the new clinic will be used to determine 6-month treatment status and viral load if available. If the transfer cannot be confirmed, the last attended and scheduled visits at the original clinic will be used to determine month 6 status.

Viral load quantification will be conducted at 6 months, consistent with WHO and Tanzanian guidelines for monitoring HIV infection. The specimen will be drawn during the 6th month of ART monitoring, formally defined as the first visit occurring after 5.5 months on ART, to accommodate variation in scheduling patterns whereby patients frequently attend a 14-day visit after ART start and monthly visits thereafter. If multiple viral load results are available for a given participant, the result nearest to 6 months on ART will be used. Viral load results from specimens collected before 5 months or after 7 months will not be used as proxies. If viral load is missing for $\geq 5\%$ of participants who are on ART at 6 months, viral suppression will be estimated for these participants using multiple imputation.

4) How many and which conditions will participants be assigned to?

Participants are individually randomly assigned to one of three conditions, including a control group and two active intervention arms:

Arm 1. Control - Standard of care: Participants in the control group receive the standard HIV primary care services according to Tanzania's National Guidelines for the Management of HIV and AIDS.

Arm 2. Intervention 1 - Standard of care plus 10,000 TZS/month: Participants receive standard HIV primary care services plus the opportunity to earn 10,000 TZS/month (~\$4.50) for up to 6 months, conditional on visit attendance.

Arm 3. Intervention 2 - Standard of care plus 22,500 TZS/month: Participants receive standard HIV primary care services plus the opportunity to earn 22,500 TZS/month (~\$10.00) for up to 6 months, conditional on visit attendance.

In both intervention arms, participants are eligible for the first cash transfer at their first follow-up visit, which is typically 14-30 days after ART initiation. After the first follow-up visit, cash transfers will be delivered a maximum of once monthly, conditional on attendance at visits spaced ≥ 26 days apart, for up to six consecutive months.

5) Specify exactly which analyses you will conduct to examine the main question/hypothesis.

i. Dose-response relationship (Question 1)

We will construct a logistic regression model: $\text{logit}(p) = a + b \cdot x$, where p is the binomial proportion virally suppressed and x is the ordinal cash amount (coded as 0, 10000, or 22500 TZS), and test our hypotheses (equivalent to $H_0: b = 0$ vs. $H_a: b \neq 0$) at $\alpha = 0.05$. We will adjust for enrollment site in the primary analysis. As a secondary analysis, we will additionally adjust for prognostic factors (age, sex, baseline WHO clinical stage). We will also test for baseline imbalance in participant characteristics (e.g., age, sex, language, education, marital status, occupation, work status, head of household, household size, food security, distance to clinic, asset index, days since starting ART, weight, WHO clinical stage) using chi-square and one-way analysis of variance tests at $\alpha = 0.05$; we will also adjust for any imbalanced characteristics in the secondary analysis. If $\geq 5\%$ of participants are missing at least one of these covariate values, we will estimate missing values using multiple imputation.

ii. Minimum effective transfer size (Question 2)

a) If a dose-response relationship exists as evaluated above, we will use the same logistic regression model to select the minimum effective transfer size, even if it is not one of the amounts tested. The point estimate on the dose-response curve corresponding to a 20% increase relative to the standard of care will be identified and considered for use in Phase 2 of the study (a cluster-randomized RCT). However, other factors will also be considered in the final decision, such as qualitative information about local denominations of currency, government and other stakeholder input, and budget considerations.

b) If a dose-response relationship does not exist OR if neither amount achieves the 20% effect size threshold, we will proceed with a direct comparison of the intervention arms. We will model the exposure as categorical transfer size (indicator variables for 10000 and 22500 TZS) and assess whether there is a difference in viral suppression between the intervention groups at $\alpha = 0.05$. We will then use the following decision rule:

1. If there is no difference between the two groups, we will use 10000 TZS for Phase 2.
2. If 10000 TZS is more effective than 22500 TZS, we will use 10000 TZS.
3. If 22500 TZS is more effective than 10000 TZS, we will apply a cost-effectiveness criterion. We will express the increase in viral suppression for 22500 TZS in terms of disability-adjusted life-years (DALYs) and determine whether the additional benefits associated with the larger transfer are worthwhile using WHO cost-effectiveness thresholds. We will then proceed with the most cost-effective value, alongside other qualitative considerations mentioned above.

6) Describe exactly how outliers will be defined and handled, and your precise rule(s) for excluding observations.

All participants will be included in the primary intention-to-treat analysis unless $< 5\%$ are missing the primary outcome (on ART and virally suppressed), in which case participants missing the outcome will be excluded; if $\geq 5\%$ of participants are missing the primary outcome, missing values will be estimated using multiple imputation and all participants will be included in the primary intention-to-treat analysis.

7) How many observations will be collected or what will determine sample size? No need to justify decision, but be precise about exactly how the number will be determined.

530 participants will be enrolled in this study, randomized, and included in the primary intention-to-treat analysis.

8) Anything else you would like to pre-register? (e.g., secondary analyses, variables collected for exploratory purposes, unusual analyses planned?)

i. Pairwise comparisons

Regardless of the results of the primary dose-response analysis, we will also report secondary pairwise comparisons between each treatment group (10000 vs. 0 TZS, 22500 vs. 0 TZS, and 22500 TZS vs. 10000 TZS). We will construct generalized linear models using the identity link for the following outcomes:

a) HIV viral suppression (< 1000 copies/ml) at 6 months on ART: As defined above in Question 3. In addition to this primary composite measure (retention plus viral suppression), we will report the components of the primary outcome: 1) retained on ART at 6 months and 2) the proportion virally suppressed out of those retained on ART at 6 months. The binomial distribution will be used for each of these outcomes to report the difference in proportions by treatment group and the variability of the difference. If the timing of the viral load test varies by group, we will include an interaction term between treatment group and timing of viral load test.

b) Appointment attendance at 6 months: The proportion of scheduled visits that were attended (within ± 4 days) during the 0–6 month period. In the event of death, any scheduled visit after the date of death will be considered not completed. If medical records indicate that a participant transferred to another clinic, the patient will be traced to the new facility and records from the new clinic will be included. If the transfer cannot be confirmed after at least 3 tracing attempts, any uncompleted scheduled visit at the original clinic will be considered missed. The Gaussian distribution will be used for this outcome to report the difference in percentage of appointments attended by treatment group and the variability of the difference.

For each of the above analyses, we will report estimates 1) adjusted for enrollment site and 2) additionally adjusted for prognostic factors (age, sex, WHO clinical stage) and any unbalanced baseline covariates.

ii. Other secondary analyses

As additional secondary analyses, we will explore effect measure modification by age, sex, socioeconomic status, time since diagnosis, and potentially other factors, however we will not be powered for these analyses.

iii. Data collection status

As indicated, we have already collected some data. We recently completed enrollment and the collection of baseline data. Nevertheless, readers may consider this a valid pre-registration because 6-month outcome data have not yet been collected for the majority of participants. Moreover, the randomization assignment has been stored in a separate file and not linked to any data collection or analysis activities.