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Implementation Science using Proctor's Framework and an adaptation of the Multiphase Optimization Strategy (MOST): Optimizing a Financial Incentive Intervention for HIV Treatment Adherence in Tanzania

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Abstract

Background: Ambitious targets have been set to end the HIV epidemic by 2030. Such targets assume that tools to end HIV exist and are successfully being deployed across populations, albeit unequally. Implementation science approaches are needed to understand the drivers of disparities and how to bring effective interventions to those most in need. We describe a hybrid implementation science approach, adapting a strategy to facilitate retention and viral suppression (VS) among PLWHIV in Tanzania.

Methods/Design: We used Proctor's framework and the multiphase optimization strategy to optimize a cash transfer to improve ART adherence and VS among PLWHIV in Tanzania. This involved three trials. The first trial tested the efficacy of cash and food assistance compared to the standard of care in improving ART adherence among treatment initiators. Cash transfers were superior to the standard of care and non-inferior, less expensive, and logistically simpler to implement compared to food. The second trial is dose-finding: identifying the optimal amount of cash for a 20% improvement in VS at 6 months. Prior to this, components were simplified to maximize reach, align with local policies, and reduce staff time. We assessed implementation science constructs to understand barriers to uptake and sustainability. Trial 3 is a cluster RCT testing the effectiveness of the optimized intervention in multiple settings.

Discussion/Implications: Our process illustrates the utility of applying multiple implementation science frameworks to arrive at an optimal implementation strategy to bridge the know-do gap with data to show efficacy and maximum potential for scalability and sustainability.

Keywords

HIV; Adherence; Retention; Cash Transfers; Tanzania; Behavioral Economics; Implementation Science

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Introduction

Although early initiation of antiretroviral therapy (ART) among people living with HIV/AIDS (PLWHIV) 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. However, in sub-Saharan Africa only 52% of PLWHIV are virally suppressed (3). Thus, achievement of UNAIDS' ambitious '90-90-90' strategy, which requires that by 2020, 90% of PLWHIV 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. 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 (4-13). Furthermore, researchers have found that by partially mitigating the detrimental consequences of poverty and food insecurity on HIV care, (14-16) financial incentives can increase the probability that PLWHIV are retained in care, adhere to ART, and have suppressed viral loads (8,17). These studies have galvanized program planners to consider financial incentives (cash transfers) as part of a comprehensive implementation strategy to increase PLWHIV engagement with care. However, despite this optimism, the efficacy of cash transfers for increasing adherence among PLWHIV has primarily been studied in controlled settings. Much less is known about factors related to the uptake and implementation of cash transfer programs for various real-world stakeholders and implementers, including what works and why, and how to improve program efficiency.

In this paper we describe an implementation science approach to iterative development of an incentive-based implementation strategy to promote ART adherence among PLWHIV in Shinyanga, Tanzania. We draw on two implementation science frameworks to answer questions that would be relevant to future scale-up and longer-term sustainability of the intervention if it is found to be effective. We used Proctor's framework (18) to define implementation constructs of interest with respect to the users, stakeholders, and context of the intervention, which were then measured using a mixed-methods approach of in-depth interviews and validated quantitative scales where applicable. In addition, we use an adapted version of the multiphase optimization strategy (MOST) framework (19) to describe our process to optimize and evaluate characteristics of the intervention itself. MOST is rooted in engineering and has been increasingly adopted as an implementation science framework to accelerate the development and rollout of effective, optimized interventions at the lowest cost possible. Given a multicomponent intervention, the 3-stage MOST framework (preparation, optimization and evaluation: see Figure 1) isolates the effective component(s) of that intervention based on pre-specified optimization criteria and an efficient study design that obviates the need to conduct large, lengthy trials. Then, the optimized intervention is evaluated for effectiveness in a subsequent RCT in a real-world setting. MOST is adaptable to various trial designs provided adherence to the key features of optimization and resource management.

Proctor's framework was identified during the study design phase to ensure inclusion of essential implementation science outcomes in research protocols. However, although the essential tenets of the MOST framework, optimization and resource management, were considerations from the very early design stages, as scalability of the implementation strategy was a goal from the beginning, the MOST framework was only identified after the research was underway. This situation is likely not uncommon; the MOST framework is under-utilized in the field of HIV and applicability of the framework to implementation science has only recently been recognized. For example, Gwadz et al. recently used the framework to design a study to isolate effective and cost-effective intervention components optimized for improving HIV viral suppression among PLWHIV of color in the US (20). We expect use of the MOST framework to increase over time in its use as an a-priori implementation science framework.

We describe a process of iterative experiments to: a) determine efficacy of the incentive-based intervention in a tightly controlled setting; b) optimize the intervention for a real-world clinical setting with a simplified implementation approach aligned with local policies; c) assess the feasibility and acceptability of the intervention package for scale up and sustainability; and d) test the optimized intervention package for effectiveness on a large scale across multiple care and treatment facilities in Tanzania. Together, this set of trials (efficacy – optimization – effectiveness) will generate an evidence base for the most effective, incentive-based ***implementation strategy*** for the clinically proven intervention of ART adherence.

Methods

The overarching research question guiding this work is whether an incentive-based approach is an effective care and treatment *implementation strategy* that will close existing gaps in the HIV treatment cascade in Tanzania. Specifically, we are interested in whether incentives can help those who recently started treatment to remain adherent over the next 6 months (a short-term cash transfer that has a definitive end), given data about attrition immediately after treatment initiation (22). To address this question, we are using an iterative trial approach (see Figure 2) to test the comparative efficacy of two distinct incentive-based interventions, optimize the intervention, simplify the delivery approach to be amenable for implementation by pharmacy staff, and test the effectiveness of the optimized intervention. Below, we briefly describe each of the trials and the implementation science frameworks that guide and describe our approach.

Trial #1: Proof-of-Concept using Comparative Efficacy (MOST Preparation Phase)

For Trial #1 (concluded in 2016, clinicaltrials.org) we used a 3-arm RCT to test the comparative efficacy of cash transfers and food assistance in improving adherence to ART. The overarching goal was to determine whether an incentive-based intervention, evaluated as two modalities, cash (22,500 TZS/month) and in-kind (food) support, could improve ART adherence as measured through the medication possession ratio (MPR), a pharmacy-based measure of adherence.(23-26) We used the following optimization criteria: cash was considered non-inferior to food assistance if the lower bound for the proportion of patients

with MPR ≥95% for the cash group was above a threshold of 10 percentage points of MPR ≥95% for the food group. This was considered to be the largest loss of effect that would be clinically acceptable when comparing cash to food assistance. 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. After 6 months, we found that short-term cash transfers were superior to the standard of care on all indicators of adherence and retention, including MPR ≥95% and loss to follow-up (17). In the cash group MPR ≥95% was 83.8% compared to the food group (79%). After 12 months, 6 months *after* the *intervention ended*, the cash group was significantly more likely to have MPR ≥95% (73.6% compared to 63.5%), remained more likely to be in care than the standard of care group and had better appointment attendance. Furthermore, cash transfers were superior to or equal to food baskets on all adherence and retention in care outcomes, were cheaper and easier to monitor, and were preferred by patients.

There were critical implementation learnings in Trial #1, beyond efficacy alone. Drawing on Proctor's framework, we understood that to advance intervention development we needed to consider how both the recipients (patients) and the eventual implementers (clinic staff) perceived the intervention. Interested in maximizing uptake among users (i.e., more patients in care) and minimizing effort among implementers, we focused on four implementation problems that we could potentially solve prior to the next phase. First, for the intervention implementation to be acceptable, feasible and sustainable, we needed to streamline patient identification and attendance monitoring. As we moved from a closely controlled research setting where research assistants were doing much of the work of identifying and monitoring patients and verifying eligibility for cash transfers to a more real-world setting where clinic staff would shoulder these tasks, we needed to minimize staff time. Second, in an effort to maximize uptake by the clinics and improve acceptability, we wanted to simplify logistics of delivering payments. In the first trial, most participants received cash transfers using mobile payment technology. However, distinct methods were required for different mobile payment vendors, and research staff who were manually sending these payments to patients needed to know what vendor each patient used so that they could receive their payment. Third, in the next phase of the research we wanted to maximize the reach of the intervention for patients by relaxing the stringent requirements for receipt of a cash transfer. In the first trial, we enforced a "hard condition" of visit attendance within a narrow window of ±4 days from the scheduled appointment in order to receive a cash transfer (27). Although this approach was suitable for a proof-of-concept study, monitoring and enforcement of the conditionality was unlikely to be feasible at scale. Thus, it was clear that the behavioral conditions for transfers had to be relaxed consistent with emerging evidence that hard conditions are likely not necessary to achieve most of the motivational effect of incentives (28). Finally, we were aware that the policy landscape with respect to ART delivery was changing in Tanzania, moving toward a differentiated care model (29). Details of how we worked through each of these problems prior to implementation of Trial #2 are presented in the next section.

Trial #2: Optimize Intervention and Implementation Model (MOST Refining Phase)

Building on the cash transfers' promising signal of effectiveness in Trial #1 and cognizant of the implementation challenges, we moved to the next phase – optimization – with viral

suppression as the primary outcome. At this point the Proctor framework outcomes were already integrated into the design and we newly recognized the similarity of our approach with MOST. Trial #2 is a Phase IIb "dose finding" study (concluding July 2019, clinicaltrials.org), with two main goals: to optimize the cash intervention using a 'dose-finding' approach (optimization phase from MOST) and to simplify the delivery model for a real-world setting in an effort to maximize uptake, improve acceptability and increase chances of scale-up (Proctor's framework). Our optimization criterion is the estimated minimum amount of cash necessary to achieve a 20% increase in the proportion of patients achieving viral suppression at 6 months. This 3-arm RCT is currently ongoing at four HIV primary care clinics in Shinyanga, Tanzania, with the following intervention groups: standard of care (SOC); 10,000 TZS/month (~$4.60) and 22,500 TZS/month (~$10.30). We included an SOC group as there was a clear need to demonstrate the effectiveness of the intervention with HIV viral suppression (VS) as the outcome of interest. Although MPR has high correlation with VS, without robust evidence on VS, the gold standard for adherence measurement, it may have been difficult to build a credible case for scale. The study enrolled 529 patients, is powered to detect a dose-response trend and will therefore provide rapid feedback, obviating the need for a lengthy effectiveness trial of various cash transfer amounts. Once the trial concludes, we will identify the best transfer size as dictated by the optimization criterion to move forward in an impact evaluation.

In order to address the implementation challenges uncovered in the Trial #1, we took the following steps prior to starting Trial #2. First, to confront the time-consuming process of patient identification and monitoring attendance and the conditions for cash transfers, and to simplify the logistics of the cash transfer payments, we created an mHealth system with biometric identification that is integrated with all mobile money providers in Tanzania. Numerous health systems, including some in Tanzania, have already implemented biometric monitoring in health systems or have plans or aspirations to do so; we built on this momentum. In collaboration with a local communication and technology firm (Rasello), we designed the system to incur minimal burden on clinic staff by using fingerprint identification linked to automated eligibility confirmation and mobile money delivery. This replaced the prior system of manually searching for each patient by their unique ID number and sending mobile money transfers via various protocols. Following the launch of the mHealth system in the study clinics, we made iterative improvements to overcome fingerprint recognition challenges related to network outages, data storage and processing limitations, and low image quality due to hardware issues, patient unfamiliarity with fingerprinting, and worn or damaged fingerprint patterns among patients who perform manual work. We are currently expanding the system capability to automatically link patient viral load results from the laboratory database of another non-governmental partner and to deliver SMS reminders; these developments will be implemented in Trial #3. As an additional benefit, visit attendance is instantly logged in the system upon biometric recognition, at which time the next appointment date is also entered by the pharmacist. The system includes alerts for key upcoming appointment dates including the 6-month viral load test, and we are currently enhancing the system to include automated notifications when appointments are missed. The system also includes automated, real-time patient clinic attendance monitoring via a secure dashboard.

Second, to maximize patient reach, we relaxed the cash transfer eligibility requirements and instead utilized a “soft condition” to receive cash. In this study, the only requirement to receive a cash transfer in the first six months of ART is that cash transfers must be spaced at least 28 days apart. This avoids the complexity and expense of strictly enforcing compliance via complex rules, as revealed in Trial #1, and was selected for several reasons. To date, most anti-poverty cash transfer programs in Africa are unconditional; conditions don’t necessarily improve outcomes; and hard conditions often exclude the worst-off beneficiaries (28). In addition, the “soft condition,” that cash transfers can only be disbursed when a visit occurs, includes an implicit “penalty” for coming late to the visit because it results in a delay in receiving the transfer. The soft condition was also an ideal choice from a behavioral standpoint: to facilitate habit formation in the first months of treatment. Habits are in part formed by cycles of cue-routine--reward (30,31), and we wanted to retain this potential benefit via the soft condition of clinic attendance. Lastly, for pragmatic reasons, clinic attendance was a natural requirement as we needed a mechanism of distribution for the cash transfers, especially for those without phones, and the clinic was a natural place to do that. Thus, the intervention evolved in response to constraints of the environment, increasing the likelihood that the intervention would be perceived as feasible and acceptable, and ultimately scalable and sustainable should the government choose to invest in this strategy.

Third, to align with HIV care guidelines in Tanzania, we targeted the cash distribution to the first six months of ART. Under the National AIDS Control Program (NACP) policy (29), if after 6 months of monthly visits patients are virally suppressed, they graduate to a differentiated care model whereby they can receive multi-months refills and do not have to visit the pharmacy themselves. Our incentive-based intervention is intended to support patients during the vulnerable first few months of treatment, bolstering Tanzania’s new differentiated care model by ensuring the intervention creates and strengthens good habits in the early months of ART.

We hypothesized that the aforementioned modifications to the delivery model will increase acceptability and scalability; to formally explore this we integrated methods to assess implementation science constructs related to the delivery model in designing Trial #2. Using the Proctor framework (27) and qualitative data collection methods, we are exploring acceptability, adoption, appropriateness, cost, feasibility, fidelity, penetration, and sustainability of the intervention, specifically the mHealth system. Additionally, we are administering structured surveys with study participants using the Health Information Technology Utilization Evaluation Scale (33) and pharmacists using the System Usability Scale (34) to understand potential barriers to scale-up and sustainability. We will use these data to guide changes to the delivery model prior to the third trial.

Trial #3: Impact Evaluation (MOST Evaluation Phase)

The team will launch a third trial in January 2020 to formally determine effectiveness of the optimized intervention in a two-arm cluster RCT in approximately half of all clinics in Shinyanga. We will test the effectiveness of the optimal cash transfer size identified in Trial #2 and implemented using the integrated, biometric mHealth system. The primary endpoint is the proportion of patients with suppressed viral load at the end of the 12- month

observation period (6 months *after* the cash transfers have ended) which will be measured among 1,984 PLWHIV initiating ART. This cluster RCT is the ultimate test of effectiveness of the incentive implementation strategy with roll-out on a broad scale to 32 clinics of varying sizes and types, allowing assessment of the strategy's success (or lack of) across multiple settings, and evaluation of factors contributing to success.

Integrated into this trial is a mixed-methods process evaluation, again using Proctor's framework (32) as a guide, but focusing on implementation challenges at scale. This will include surveys and in-depth interviews with clinic staff, clinic observations, and exit interviews with study participants. Finally, an economic evaluation will be conducted using a micro-costing approach.

Discussion

It is increasingly recognized that implementation science approaches to the design and evaluation of HIV-related programs are essential to achieve UNAIDS' 90-90-90 goals (35). This is evidenced by a burgeoning literature on implementation science frameworks (32,36-38) and methodology (19,39-42) and underscored by a shift in the global health discourse to be inclusive of scholarship focused on bringing evidence-based programs and policies to scale. Consistent with this viewpoint, we described a multi-study, iterative, implementation science approach to development of an incentive-based intervention to promote ART adherence among PLWHIV in Shinyanga, Tanzania. We used Proctor's framework (32) to define key implementation constructs measured at multiple levels of the system, including the patient, healthcare worker, organization, and political. Contemporaneously, we used an adapted version of the MOST framework (19) to describe our iterative approach to optimize and evaluate the characteristics of the intervention itself. Together, this process led to a large-scale effectiveness study of a refined intervention optimized for multiple stakeholders that will soon be evaluated in multiple clinics in Tanzania.

This case study holds value for the broader health community beyond the specific details of how to optimize an incentive-based program to improve HIV adherence. First, the value added by considering implementation issues from the beginning of the project is clear. Without a thorough understanding of implementation science-related constructs as they pertain to multiple stakeholders, the likelihood of effectiveness in a real-world setting and successful scale-up and sustainability is small (38). While this paper represents a post-hoc application of the MOST framework, implementation science constructs were front of mind during development of these trials, and in fact Proctor's framework was included in the original grant application and study design. Evidence for the effectiveness for cash transfers on a range of HIV-related outcomes is growing (4-14,16,27). However, the remaining, policy-relevant questions address how to bring this evidence-based strategy to scale in a particular environment. Early on in the research, there were important concerns raised by stakeholders about workflows at the clinic, reach and inclusiveness of the intervention, alignment with changing NACP policies, and logistics of cash disbursement and patient tracking that warranted focused attention on scale and sustainability (beyond funding) - similar to the situation for numerous other interventions, such as PrEP and HIV self-testing.

For this reason, implementation constructs should be identified and measured during the development and pilot stages of any new intervention, alongside parallel processes to determine efficacy. Fortunately, implementation science frameworks and methodologies are easily paired with traditional quasi-experimental and experimental studies, including hybrid designs that evaluate effectiveness and implementation strategies simultaneously (39,42).

In addition, the implementation science approach to intervention development, refinement, and evaluation described here is well-aligned with the growing number of interventions that leverage advances in behavioral science (including behavioral economics). A distinguishing feature of these motivational approaches (e.g., incentives, commitment devices, social norms) is that there are often multiple ways to implement a single strategy. For example, incentives can be implemented as cash, in-kind support, or a lottery; commitment devices can include both mutable and immutable consequences; and there are myriad ways of using social norms to influence behavior. In understanding how to most effectively draw from this toolbox of behavioral economics interventions to improve HIV outcomes, iterative implementation science approaches, like that posed in the MOST framework, will be necessary. We have described one such iterative approach; other study designs such as sequential, multiple assignment randomize trials (SMART) and factorial designs can facilitate isolation of the optimal components of a multi-component intervention for a given behavior change intervention or to ascertain the most effective sequencing or adaptation of interventions to account for heterogeneous responses to interventions.

In conclusion, we have presented a real-world example of how the incorporation of implementation science frameworks can enhance traditional epidemiologic studies by simultaneously refining and optimizing an intervention while remaining committed to rigorous measurement of effectiveness. To fill implementation gaps, particularly in low-resource settings that have been hit hardest by the epidemic and are often slowest in receiving the newest tools for prevention and treatment of HIV, iterative implementation science approaches are needed to understand how to efficiently bring effective interventions to those who need them most.

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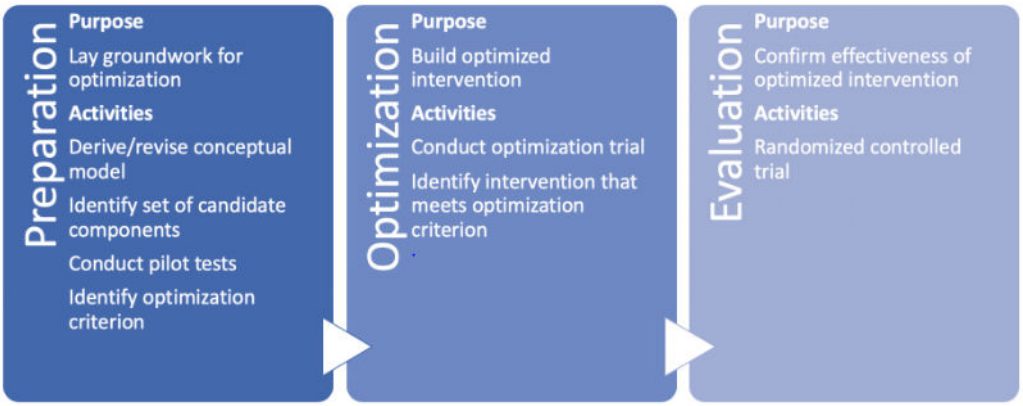

Figure 1.
Phases of the MOST Strategy, adapted from Collins et al. (43)

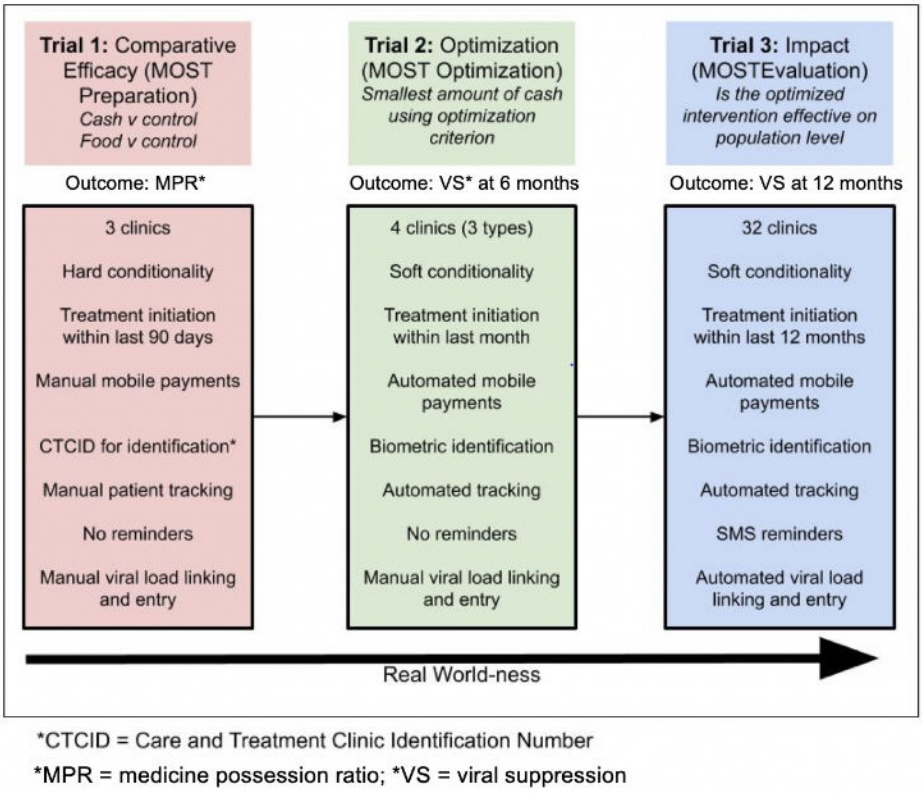

Figure 2.
Sequential trial strategy based on the MOST framework