Conditional economic incentives to improve adherence to antiretroviral therapy: effectiveness and implementation considerations

by

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Abstract

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Increasing evidence demonstrates that short-term conditional economic incentives may improve adherence to antiretroviral therapy (ART) for people living with HIV, thereby conferring individual health benefits and preventing transmission. However, few previous studies have assessed viral suppression, a biomarker of adherence and the ultimate goal of HIV "treatment as prevention" efforts. Moreover, questions remain around pathways of impact, best practices for real-world implementation, and durability of effects. For example, there is a lack of coherent evidence indicating whether such incentives mitigate food insecurity, an underlying barrier on the hypothesized pathway between economic incentives and ART adherence. Additionally, essential details for scaling up implementation remain largely unexplored, including optimal design and distribution aspects that can affect scalability. Finally, the short follow-up period for most prior studies inhibits understanding of any long-term harms or benefits of time-limited incentives. To address these gaps, this work studied the effects of cash and food incentives in two randomized trials of adults initiating ART in rural Tanzania. It evaluated outcomes including food insecurity, viral suppression, and long-term retention in care, and investigated the roles of incentive size and delivery mode.

Chapter 1 assessed effects of short-term cash and food incentives for HIV care on food security, nutrition, and livelihoods. This analysis used data from a 2013-2016 study of 800 food-insecure ART initiates at three HIV primary care clinics in Shinyanga region, Tanzania. Participants were randomized to receive usual HIV care (control group) or to additionally receive cash or food transfers for up to 6 consecutive months, conditional on timely attendance at scheduled clinic visits. The primary study results demonstrated that both cash and food incentives increased medication possession and retention in care at 6 and 12 months compared to the control group. The analysis herein found that food security, nutritional status, and work status improved over time in all groups, potentially due to the benefits of ART on physical health and the ability to work. Incentives further reduced severe

food insecurity at 6 months relative to usual care but had no effects on these other measures at 6 or 12 months. These results suggest that alleviating severe short-term food insecurity via a modest income effect is one plausible pathway for incentives to bolster ART adherence. The lack of impact on other outcomes indicates that small incentives likely operate primarily via a price effect, lowering costs associated with clinic attendance. Moreover, the overall improvements in well-being after starting ART underscore the importance of strategies to support adherence both for ending the HIV epidemic and strengthening livelihoods.

Chapter 2 evaluated impacts of two different sized financial incentives for HIV care on viral suppression. A randomized trial was conducted at four health facilities in Shinyanga region, Tanzania (2018-2019), whereby 530 adult ART initiates were randomized to receive usual HIV care or to additionally receive a financial incentive for monthly clinic attendance in the amount of 10000 (US $4.50) or 22500 (US $10) Tanzanian Shillings for up to 6 months. Mobile health technology (mHealth) was used to implement biometric attendance monitoring linked to automated electronic payments. The study found that both incentive amounts improved viral suppression at 6 months, with a trend toward larger effects with increasing incentive size. As the first randomized trial to evaluate the impact of clinic-based financial incentives for treatment-seeking behavior on HIV viral suppression in a low- or middle-income country, these findings contribute critical evidence for understanding the promise of financial incentives to improve HIV treatment adherence.

Chapter 3 ascertained the long-term effects of time-limited incentives for HIV care. Individuals who had participated in the previous study of cash and food incentives in Tanzania were followed up after 3 years had elapsed since enrollment in the original trial. These former participants were located using gold-standard tracing procedures including phone calls, home visits from community health workers, and triangulation with other facilities. Clinic attendance records obtained at follow-up were used to measure retention in care and mortality at 24 and 36 months. Contributing to the scientific gap regarding long-run incentive effects, the results showed no significant differences between study groups in retention or mortality, indicating neither lasting benefit nor eventual harm from short-term incentives.

Together, these findings contribute an improved understanding of the effectiveness and optimal implementation of conditional economic incentives to promote HIV treatment adherence. The short-term effects on food insecurity show that incentives may help stabilize vulnerable households at the time of ART initiation, thereby supporting improved adherence. Next, the viral suppression results definitively show that incentives have impact on a biological measure of ART adherence, and that these effects can be achieved using mobile health technology to deliver incentives. A trend toward increasing effectiveness with larger incentives was established, while even the smallest incentive tested resulted in significant improvement over the standard of care. Lastly, the long-term results found no eventual harm from incentives, while benefits gradually reduced over time. These findings demonstrate that economic incentives are a safe and effective strategy to promote adherence at the time of ART initiation, adding a major contribution to evidence-based approaches to ending the HIV epidemic.

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Introduction

Health systems and the social determinants of health

Global efforts to improve population health and reduce health inequities increasingly emphasize the role of social determinants of health (SDH). The World Health Organization's Commission on the Social Determinants of Health (WHO CSDH) defines SDH as the social, political, economic, and cultural conditions in which people live and work and the structural drivers of these conditions. The WHO CSDH conceptual framework (Figure 0.1) relates structural determinants (social, economic, and political context and socioeconomic status) to intermediary determinants (material circumstances, behaviors and biological factors, and psychosocial factors), which in turn influence health and well-being.[1] Importantly, the framework identifies the health system itself as a social determinant of health. The health system can mitigate inequities by improving access to care and facilitating intersectoral action to improve population health. Health systems also mediate the heterogeneous effects of illness of livelihoods, with the capacity to intervene on the feedback cycle between poor health and worsening of structural determinants.

Although the SDH framework was recently formalized, several countries in Latin America began acting on these ideas in the late 1980s with social sector reforms, including the expansion of universal health coverage to strengthen health systems and promote equitable access and outcomes.[2] Many of these countries financed supply-side approaches to expand health insurance and scale up health services. In addition, they implemented demand-side interventions including large-scale conditional cash transfer programs to encourage uptake of health services and target poverty alleviation. These programs generated evidence that the design, operations, and financing of health systems have powerful implications for population health. Highly influential impact evaluations such as that of Mexico's *Progresa* program (later known as *Oportunidades* and now *Prospera*)—which found substantial improvements in both child and adult health resulting from a national cash transfer program incentivizing engagement in primary health care, nutrition monitoring and supplementation, and health education programs[3]—sparked interest worldwide in this intervention approach, both for poverty alleviation and for behavior change. As conditional cash transfer programs have spread around the world, a related body of literature has rapidly grown that focuses on

discrete interventions offering smaller, short-term incentives targeted at specific health behaviors and outcomes.

This dissertation applies the SDH framework to the circumstances of people living with HIV (PLHIV). It investigates the role of small, time-limited incentives distributed through the health care system to improve health and well-being, with overarching goal to reduce health inequities related to HIV/AIDS.

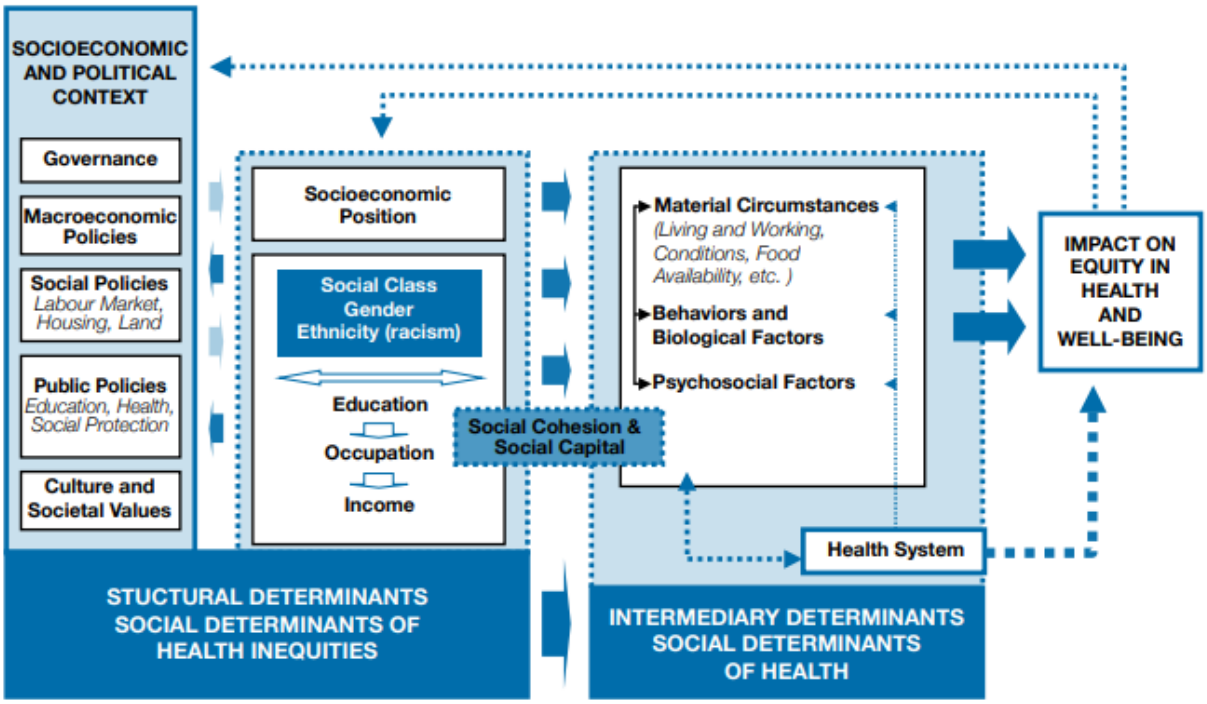

Figure 0.1: WHO Social Determinants of Health Conceptual Framework (Solar & Irwin, 2010)

Food insecurity and HIV

The HIV/AIDS epidemic is deeply intertwined with social determinants of health, manifesting in an uneven burden of disease shaped by factors such as poverty, inequality, and discrimination. In recent years, supply-side initiatives have significantly expanded access to antiretroviral therapy (ART) for PLHIV around the world. The ambitious UNAIDS 90-90-90 goal aimed for 90% of PLHIV to know their HIV status, for 90% of those diagnosed with HIV infection to receive sustained ART, and for 90% of those on ART to have viral suppression by 2020 (since elevated to 95-95-95 by 2030). This expansion followed groundbreaking evidence that viral suppression through ART provides not only individual clinical benefits, but also prevents onward HIV transmission.[4] However, achieving the level of viral suppression

necessary to realize these benefits relies on early engagement in care and continuous high treatment adherence. The 95-95-95 goal remains elusive in many countries such as Tanzania, where only 66% of PLHIV are on ART and only 75% of these (48% of all PLHIV) are virally suppressed.[5]

As researchers investigate demand-side gaps and strategies, growing attention has focused on the role of food insecurity as a barrier to ART adherence. Food insecurity manifests when "the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain."[6] In sub-Saharan Africa, where an estimated 67% of 38 million people living with HIV globally reside,[7] nearly a third of the population experiences severe food insecurity.[8] It is critical to address food insecurity in the context of HIV/AIDS due to the syndemic overlapping burdens and additive effects of food insecurity and HIV in which one condition exacerbates the other.[9–11]

Building on the work of Ivers *et al.* (2009) and others, Weiser *et al.* (2011) developed a conceptual framework of the linkages between food insecurity and HIV/AIDS (Figure 0.2).[9, 10] They theorize that structural drivers (ecological, economic, and social factors) give rise to food insecurity, which in turn influences both the acquisition of HIV/AIDS and related morbidity and mortality. Herein the focus is on the latter mechanisms, in order to understand barriers and inform interventions to support treatment adherence for people living with HIV.

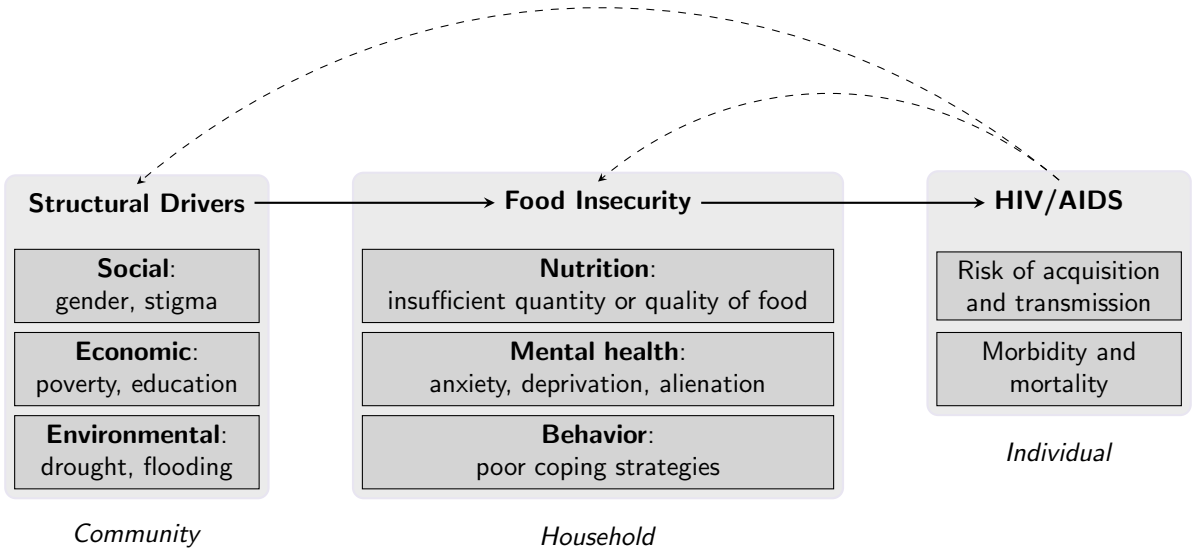

Figure 0.2: Conceptual framework for food insecurity and HIV/AIDS linkages (adapted from Weiser *et al.*, 2011)

According to the conceptual framework, food insecurity shapes HIV/AIDS morbidity and mortality through three pathways, each of which involve ART adherence: 1) nutritional pathways; 2) mental health pathways; and 3) behavioral pathways (Figure 0.3).[10]

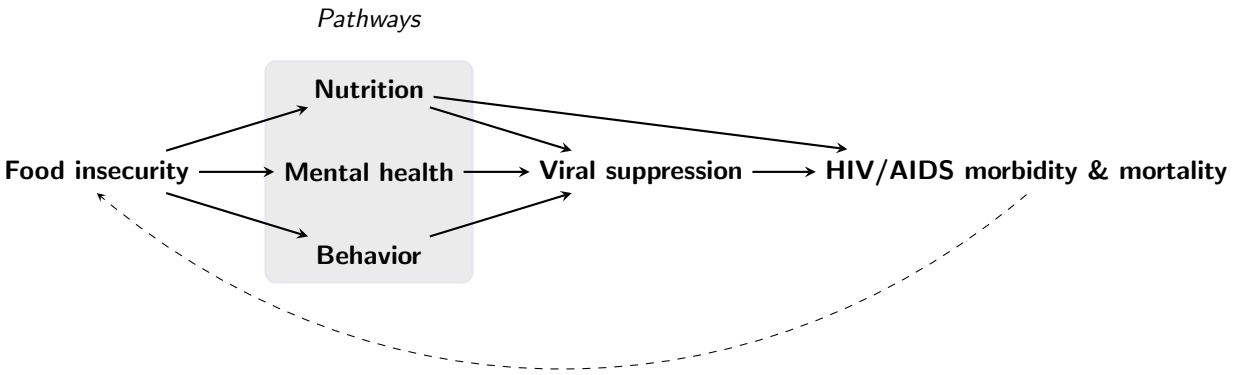

Figure 0.3: Food insecurity and HIV/AIDS morbidity and mortality (adapted from Weiser *et al.*, 2011)

Nutritional pathways

Insufficient quantity and quality of food can lead to macronutrient and micronutrient deficiencies, which are both associated with an increased risk of HIV-related morbidity and mortality.[12, 13] Driving factors include a 10%-30% increase in energy requirements for PLHIV[14] and HIV-related malabsorption and diarrhea,[15] whereby lack of access to appropriate foods can further cascade into nutrient deficiency, weight loss, accelerated disease progression, and mortality.[9, 16] Weakened health status may also limit the ability to attend facility-based HIV care and thereby negatively impact ART adherence.

Mental health pathways

Food deprivation and anxiety about the ability to acquire acceptable foods in socially acceptable ways can have mental health consequences such as depression. Indeed, food insecurity is strongly associated with poor mental health status, including among PLHIV.[17, 18] In turn, depression and anxiety have been linked to lower uptake and adherence to ART and worse HIV-related outcomes.[19]

Behavioral pathways

Food insecurity and poverty can also directly influence non-adherent behaviors due competing resource demands between food and medical care. Time spent obtaining food (e.g., through physically demanding subsistence agriculture or other activities in exchange for

money or food) may interfere with medication adherence and/or appointment attendance. Costs of clinic attendance—including transportation fees and opportunity costs of time away from work—may pose substantial barriers in resource-constrained settings. Additionally, food-insecure patients may avoid ART due to greater side effects experienced in the absence of food.[20, 21]

At the same time as food insecurity contributes to HIV/AIDS through these pathways, HIV intensifies food insecurity by inhibiting the ability to engage in livelihood-generating activities if/when an individual becomes symptomatic,[22] increasing medical cost burdens,[23] and weakening social support due to stigma.[24] The result is a vicious cycle of food insecurity and HIV/AIDS morbidity. This multifaceted relationship between food insecurity and HIV/AIDS necessitates an integrated response to HIV and food insecurity. Supported by a decade of research demonstrating that food insecurity undermines treatment adherence, researchers and policymakers have recommended interventions to mitigate food insecurity in order to improve ART adherence.[25, 26] Examples of these interventions will be discussed in the next section, with a focus on "provision-type" incentives such as cash and food transfers.

Provision incentives for treatment adherence

As the importance of food security and nutrition for PLHIV has gained recognition, national governments and international organizations have begun incorporating food security and nutrition programming into HIV/AIDS service provision.[22, 27] Under the SDH framework, these intersectoral actions by health systems hold promise to improve health equity by intervening on the cycle of food insecurity and ART non-adherence. However, few of these programs have been rigorously evaluated, with a particular dearth of evidence in low- and middle-income countries (LMICs).

Recent small-scale studies have contributed to this gap by demonstrating that short-term interventions targeting food insecurity can improve adherence. The majority of these interventions have administered incentives tied to clinic attendance in the form of cash[28] or food [28–33] assistance. Within a sustainable livelihoods framework, short-term cash and food transfers are "provision" interventions intended to meet basic needs and help stabilize vulnerable households,[34] such as those where an adult household member is starting ART coupled with the experience of stress and economic shock due to potential recent HIV diagnosis, stigma, illness, and loss of productivity.[35] Other interventions aimed at "protection" (e.g., income-based safety nets) and "promotion" (e.g., microenterprise development) may be better suited for supporting food insecurity at times of less acute vulnerability.[34] For example, a 12-month pilot intervention for patients on ART in Kenya that provided a water pump, microfinance loan, and education in farming and financial management found improvements in viral suppression and food security,[36] although preliminary evidence from a follow-up study indicates that such intensive interventions may be difficult to scale.

While increasing evidence demonstrates the power of incentives to improve short-term ART adherence, uncertainty remains regarding effects on the underlying barrier of food insecurity and the ability of incentives to interrupt the bi-directional relationship between food insecurity and HIV. Moreover, questions remain about the mechanisms through which incentives operate (i.e., by alleviating food insecurity or other pathways), the sustainability of effects from short-term interventions, and how to optimize design components including transfer size and delivery mode for effective implementation. The following sections will discuss each of these considerations.

Pathways through which incentives operate

Food insecurity

Understanding the pathways through which incentives operate is important for designing effective and appropriately targeted interventions. Mitigating the barrier of food insecurity, given an incentive of sufficient size that is utilized for household food supply and/or alleviates anxiety about household food supply, is one of several possible ways in which incentives could improve ART adherence (as discussed below). However, many of the studies that found positive effects of incentives on retention and adherence also examined food security, and provided mixed findings for this outcome.

In terms of food incentives for retention and adherence to HIV care, four observational or quasi-experimental studies were previously conducted among patients on ART in LMICs, all of which found improvements in retention and adherence associated with food support. Two found no association with nutritional status,[29, 32] one found improved food security and nutritional status,[30] and one found improved food security but worsened nutritional status in the form of increased BMI among a population with high obesity.[37] One additional study found that food assistance improved food security and BMI among ART-naïve patients but had no effect among patients on ART.[38] The lack of randomization in these studies precludes inference about whether the intervention caused the observed outcomes. Inconsistencies may also derive from differences in sample size and characteristics, attrition from study follow-up, intervention timing in relation to starting ART, follow-up time, and transfer sizes.

In terms of cash incentives, no prior studies in LMICs have quantitatively evaluated the effects of short-term conditional cash incentives on food security or nutrition among patients on ART, although large-scale conditional cash transfer programs aimed at poverty alleviation have demonstrated success at improving nutritional status among various populations.[39] Additional research is needed to understand the effects of cash and food incentives on food insecurity and nutrition as potential intermediates of ART adherence.

However, mediating food insecurity is just one possible mechanism for the effects of incentives on ART adherence. According to neoclassical and behavioral economic theory, incentives may operate through several pathways including price and income effects as well as psychological effects.

Price and income effects

Conditional transfers, such as those provided in the aforementioned studies, can operate via an *income effect* of increased economic wellbeing or via the *price effect* whereby it is more "expensive" not to attend the clinic.[40] An income effect could increase adherence by directly alleviating the barrier of food insecurity if households have more purchasing power that can be directed to food. Alternatively—or additionally—a price effect could improve ART adherence by increasing motivation to visit the clinic and by mitigating associated attendance costs including transportation, clinic fees, and time spent at the clinic.

Extrinsic & intrinsic motivation

Incentives may also operate by providing "extrinsic" motivation to engage in an activity in order to earn a reward. There has been concern that increasing extrinsic motivation could crowd out "intrinsic" motivation[41] and that short-term incentives could lead to reference dependence,[42] leading individuals become unwilling to engage in a behavior for which they were previously rewarded. However, evidence from field research fails to support these ideas.[43] On the contrary, some studies suggest that extrinsic motivations may actually *activate* intrinsic motivation and promote habit formation,[44, 45] including among PLHIV receiving cash and food incentives.[46]

Overcoming present bias

Another possible pathway through which incentives may operate involves individuals' tendency to place greater value on near-term benefits as opposed to future benefits.[47] This "discounting" is particularly relevant in the case of ART adherence, where the clinical benefits are not immediately realized and the future societal benefits of reduced transmission have limited individual salience. Incentives can help to change behavior by bringing benefits into the present, particularly when delivered on a frequent basis.

In summary, further research into the secondary effects of incentives for ART adherence—including impacts on food insecurity—is needed to understand the pathways through which incentives operate. This knowledge will help to inform when and for whom incentives may be appropriate, provide insight into the expected durability of effects, and indicate what kind of additional support may need to be packaged together with incentives to improve durability.

Durability of effects from short-term incentives

Studies of time-limited incentives for improving ART adherence have found substantial short-term benefits.[28–33] However, as none of these studies examined the long-term effects (>6 months) of incentives after removal, any durable benefits or eventual harms (e.g., from reduced intrinsic motivation as described above) remain unknown. There are several mechanisms through which short-term incentives could generate sustained ART adherence, including improvements in food security and habit formation.

Feedback cycle of food security and ART

Because ART adherence and food security are mutually re-enforcing, interventions that result in high adherence (such as incentives) hold potential to initiate a positive feedback cycle that sustains future adherence and food security. For example, even without financial or in-kind support, improvements in food security and nutritional status have been observed among patients beginning ART.[48, 49] These findings have been attributed to the benefits of treatment on physical health among patients afflicted with HIV-related illness, in turn enabling individuals to return to livelihood-generating activities and attain greater food security. For example, a study in Uganda found that ART was related to improved food insecurity via improved functioning and ability to work.[48] Upon mitigating the barriers of food and economic insecurity (e.g., through cash or in-kind transfers), patients may be more likely to remain adherent to ART and to re-enter the labor force, thereby theoretically reducing or obviating the need for continued support.

Habit formation

Even without improvements in food insecurity, short-term incentives may produce sustainable change by promoting habit formation. Contrary to concerns about crowding out internal motivation, Charness and Gneezy (2009) found that cash incentives for gym attendance resulted in continued attendance even after payments were discontinued.[44] Dupas (2014) found that short-term subsidies for antimalarial bednets produced a greater willingness to pay for bednets in the future.[45] Timing the provision of cash and food incentives at the start of ART initiation, as in the studies herein, may facilitate habit formation that leads to lasting adherence, even after incentives are withdrawn.

Through these theoretical pathways, the demonstrated effects of incentives on short-term adherence may lay the groundwork for sustained adherence by improving physical health and food security while helping new patients develop adherence habits. However, of the previously cited studies that found effects of incentives on adherence, most only followed participants for 6 to 12 months and did not measure effects after incentives were withdrawn. A predominance of short-term studies precludes our understanding of the durability of benefits or any eventual harms from time-limited cash or food incentives.

Optimizing incentive design and implementation

While preliminary research on incentives for ART adherence has delivered promising results, many details remain unclear with respect to translating these findings from controlled study settings into real-world implementation. The specifics of incentive design and distribution may have a large influence on outcomes. In particular, the size and delivery mode may play important roles in the effectiveness and efficiency of short-term cash and food incentives for PLHIV.

Incentive size

Larger incentives may provide stronger motivation all else constant, however behavioral economic theory suggests that timing and salience are important factors.[47] For example, small and frequent incentives may outperform large, one-time transfers by ensuring that benefits are felt in the present rather than discounted future rewards.[50, 51] The feasibility of real-world implementation given resource constraints must also be considered in determining incentive size. Calibrating the incentive size to the minimum effective amount would ensure efficient use of resources and maximize reach. However, across the incentive literature there are few examples of studies comparing different incentive sizes.[47] Research on the optimal incentive size is an important next step to scaling up incentives for ART adherence.

Delivery mode

A further consideration for implementing incentives is an appropriate delivery system. In particular, the logistics of distributing incentives through health care systems may pose challenges given a shortage of staff with competing time demands. To the extent that incentives can improve viral suppression, reduce HIV-related complications, and even reduce transmission, the benefits from incentives may reduce the burden of HIV on health care systems. However, some health professionals oppose reorientation of health systems to address the social determinants of health, arguing that this additional responsibility is beyond the capacity of an already overstretched healthcare workforce.[52] Thus, successful adoption of incentive delivery within health systems will require a simple distribution mechanism. The use of mobile technologies to support the achievement of health objectives (mHealth), including biometric monitoring and mobile payment systems, offers the potential for seamless integration of incentives into health service delivery. Digital technologies are increasingly used for cash-based transfers in humanitarian settings, supporting a shift from food *aid* to food *assistance* that respects individual autonomy.[53] As the area of mHealth is relatively new and rapidly growing, research on the potential of these technologies for optimizing incentive delivery is needed.

Summary

Conditional economic incentives hold promise for mitigating socioeconomic barriers and improving adherence to ART among people living with HIV, however key aspects of effectiveness and implementation have not been previously studied. Herein, Chapter 1 explores pathways to adherence through food security, nutrition, and employment. Chapter 2 ascertains effects on viral suppression as a biological measure of adherence, compares multiple incentive amounts to elucidate the optimal size, and tests the feasibility of using mHealth for incentive delivery. Chapter 3 assesses the long-term harms or benefits of short-term incentives. Together, this work contributes to an improved understanding of effectiveness and implementation of conditional economic incentives to improve ART adherence, establishing the value of this approach as part of a comprehensive strategy to ending the HIV epidemic.

Chapter 1

Pathways to adherence

Effects of short-term cash and food incentives on food insecurity and nutrition among adults with HIV in Tanzania: a three-arm randomized controlled trial

Summary

Background Food insecurity impedes antiretroviral therapy (ART) adherence. A previous study found that short-term cash and food incentives increased ART possession and retention in HIV services in Tanzania. To elucidate potential pathways that led to these achievements, this analysis examined whether incentives also improved food security. **Methods** In a 3-arm randomized controlled trial conducted at 3 clinics from 2013 to 2016, 805 food-insecure adult ART initiates ($\leq$90 days) were allocated (3:3:1) to receive cash or food transfers ($11/month for $\leq$6 months, conditional on visit attendance) or usual care (control). Changes from baseline to 6 and 12 months were assessed in: food insecurity (severe; access; dietary diversity), nutritional status (body weight; body-mass index), and work status. Difference-in-differences average treatment effects were estimated using inverse-probability-of-censoring weighted longitudinal regression models. **Findings** The modified intention-to-treat analysis included 777 non-pregnant participants with 41.6% severely food insecure. All three study groups experienced improvements from baseline in food security, nutritional status, and work status. After 6 months, severe food insecurity declined within the cash [-31.4 percentage points (pp) to 11.5%] and food (-30.3 pp to 10.4%) groups, but not within the control group. Relative to the control, severe food insecurity decreased by an additional 24.3 pp for cash (95% CI: -45.0, -3.5) and 23.3 pp for food (95% CI: -43.8, -2.7). The interventions did not augment improvements in severe food insecurity at 12 months, nor food access, dietary diversity, nutritional status, or work status at 6 or 12 months. **Interpretation** Small cash and food incentives provided at treatment initiation may mitigate severe food insecurity. These effects may have facilitated previously observed improvements in ART adherence.

1.1 Background

Despite expansion of access to antiretroviral therapy (ART) around the world, persistent food insecurity and undernutrition impede efforts to stem the HIV/AIDS epidemic.[10] Food insecurity manifests when "the availability of nutritionally adequate and safe foods or the ability to acquire acceptable foods in socially acceptable ways is limited or uncertain."[6] It is critical to address food insecurity in the context of HIV/AIDS due to bidirectional links between food insecurity and HIV in which one condition exacerbates the other.[10]

For example, food insecurity undermines treatment adherence through multiple mechanisms, including greater side effects experienced in the absence of food and competing resource demands between food and medical care.[20, 21] Food insecurity adversely impacts overall nutritional and health status among HIV-infected adults due to their 10%-30% increase in energy requirements.[14] Combined with HIV-related malabsorption, lack of access to appropriate foods can further cascade into nutrient deficiency, weight loss, accelerated disease progression, and mortality.[9, 16] At the same time, HIV intensifies food insecurity by reducing the ability to engage in livelihood-generating activities,[22] increasing medical cost burdens,[23] and weakening social support due to stigma.[24]

To achieve UNAIDS goals to improve HIV treatment access and adherence as part of a global epidemic control strategy,[54] there exists an urgent need for integrated responses to HIV and food insecurity. This approach is especially important in sub-Saharan Africa, where an estimated 67% of 38 million people living with HIV globally reside[7] and nearly a third of the population experiences severe food insecurity.[8] However, few studies have rigorously evaluated the effects of food security interventions for people living with HIV, with a particular dearth of evidence in low- and middle-income countries.

To address this gap, short-term cash and food assistance was compared to the standard of care among food-insecure adults initiating ART in Tanzania. Previous results found that 85.0% of the cash group and 79.2% of the food group achieved high levels of ART adherence during the 6-month intervention period using a pharmacy-based measure of adherence, both of which were higher than the standard of care (64.3%).[28] To elucidate potential pathways that led to these achievements, this analysis examines whether cash and food incentives also improved food security, nutritional status, or participation in livelihood-generating activities.

1.2 Methods

Study design and participants

A three-arm parallel-group randomized controlled trial was conducted in Shinyanga, Tanzania to evaluate the effects of short-term conditional cash and food assistance among people living with HIV. Study procedures have been previously described[28, 55] and the trial was

preregistered (ClinicalTrials.org, NCT01957917). Briefly, patients initiating treatment at three HIV primary care clinics were individually randomized to receive standard-of-care ART services (comparison condition) or to additionally receive one of two interventions: conditional cash transfers or food baskets.

Participants were recruited using the following inclusion criteria: adults aged 18 years or older; initiated ART within the previous 90 days; and food insecure, according to the Household Hunger Scale (score $\geq$2).[56] Severely malnourished patients (BMI <16 kg/m^2) were excluded due to their need to receive special nutritional and clinical support for recovery. During the recruitment time period (2013-2015), national guidelines restricted ART eligibility among non-pregnant adults to individuals with CD4 cell count <350 cells/µL.[57] After screening, eligible individuals provided written informed consent to participate in the study.

Cash or food assistance was provided monthly for up to six consecutive months, conditional on attending scheduled clinic visits which were typically monthly. The cash transfer was 22 500 Tanzanian Shillings per month (approximately $11 USD). The food basket was equivalently valued and designed to supplement the household food supply, including whole maize meal (12 kg), groundnuts (3 kg), and beans (3 kg). Each clinic also provided nutrition assessment and counseling to all patients through the President's Emergency Plan for AIDS Relief Nutrition Assessment, Counseling, and Support program.[58]

Study staff conducted clinic-based interviews and medical record abstraction at baseline and approximately 6 (range: 5–10) and 12 (10–20) months among participants who continued attending HIV care at the same clinic. Interviews were conducted in Kiswahili and assessed food security, labor force participation, and other socio-demographic characteristics. Medical record abstraction included body weight, height, CD4 count, and WHO Clinical Stage.

The Tanzania National Institute for Medical Research and the Committee for Protection of Human Subjects at the University of California, Berkeley approved this study.

Measures

Primary outcomes include changes in food security and nutritional status from baseline to 6 months. Secondary outcomes include changes in food security and nutritional status from baseline to 12 months, and changes in livelihood-generating activities from baseline to 6 and 12 months.

Food security

Food security was assessed via interview using three validated and widely used scales, each constructed following official guidelines: food deprivation using the Household Hunger Scale (HHS);[56] food access using the Household Food Insecurity Access Scale (HFIAS);[59, 60] and diet quality using the Individual Dietary Diversity Score (IDDS).[61]

The HHS and HFIAS are household-level indicators consisting of occurrence and frequency-of-occurrence questions (rarely, sometimes, or often) about experiences affecting household members in the past four weeks. The HHS includes three items about insufficient food intake (e.g., someone went to sleep at night hungry), scored from 0 to 6 and categorized as little to no hunger (0–1), moderate hunger (2–3), or severe hunger (4–6); the first two categories were collapsed to focus on changes in the proportion with severe HHS. The HFIAS includes the HHS and six additional items capturing anxiety about the household food supply and insufficient food quality, scored from 0 to 27 (with a higher score indicating greater food insecurity).

The IDDS is an individual-level measure about nutritional quality of the diet. It asks participants to recall the foods eaten yesterday or the last typical day, with responses categorized into nine food groups and summed to create a score with maximum of nine.

Nutritional status

Nutritional status was evaluated as body weight (kg) and body-mass index (BMI, kg/m^2), using patient height and weight measurements abstracted from clinic-based records. Clinic staff measured height at treatment initiation and weight at each clinic visit.

Livelihood

The proportion engaged in livelihood-generating activities was assessed via interview. Measures included labor force participation (currently working) and functional limitation (inability to do work or housework due to illness in the past year).

Statistical analysis

First, the baseline balance of participant characteristics by group was evaluated using chi-square and one-way analysis of variance tests. Next, multivariable longitudinal regression models were constructed for each outcome using inverse-probability-of-censoring weighted generalized estimating equations (IPCW-GEE) to account for repeated measures and attrition.[62] IPCW is a well-established method to reduce bias from attrition by up-weighting observed participants who have similar characteristics to missing participants. Weights were constructed using a priori specified predictors of attrition including study group, clinic, month and year enrolled, socio-demographics, baseline outcome values, and medication possession ratio (MPR) $\geq$95% from 0-6 months or 0-12 months as a measure of adherence (Table A.1).[63]

To evaluate mean differences in outcomes, all models used the Gaussian distribution and identity link and included terms for assigned intervention group, follow-up period, and intervention-period interaction. Covariates including clinic and factors imbalanced at base-

line were included in each model, along with baseline characteristics known to be associated with food security and nutritional status to increase precision.[64, 65]

Using these models, within-group changes from baseline to 6 and baseline to 12 months were assessed as the linear combination of terms for period and period-by-group interaction. Next, the difference-in-differences average treatment effect (ATE) between groups was evaluated as the period-by-group interaction term for each follow-up period.[66] Pairwise comparisons of the three groups were assessed using a Wald test with alpha=0.05 and Bonferroni's correction for multiple comparisons.

All participants were included in primary analyses as contributors to baseline estimates, regardless of censoring status. As a sensitivity analysis, unweighted complete-case outcomes were calculated among the sub-population of participants observed at both baseline and 6 months. The primary analyses were also repeated a) without excluding pregnant women, b) without adjustment for covariates, c) using stabilized weights,[67] and d) excluding adherence (MPR) from the weights so as to only include baseline predictors. Analyses were performed with Stata version 14.2 (College Station, Texas, USA).

1.3 Results

Sample characteristics

As previously described,[28] 805 participants were recruited and randomized from December 2013 to July 2015 (Figure 1.1). Subsequently, 5 individuals with no follow-up time (transferred, died, or opted out before their next scheduled visit or had no medical records) were excluded. For this analysis, 23 women who were pregnant at baseline (Table A.2) were additionally excluded due to their unique biopsychosocial circumstances, resulting in a modified intention-to-treat (mITT) population of 777 participants.[68]

Participants were majority female (62.6%) with a mean age of 37 years at the time of enrollment (Table 1.1). All participants were food insecure as per eligibility criteria and 41.6% had experienced severe food insecurity in the past 30 days. The mean BMI was 21.4 kg/m^2 with 16.2% underweight (<18.5 kg/m^2). Just over half (58.4%) were working, 55.9% had experienced functional limitation due to illness in the past year, and 58.2% were classified as WHO Clinical Stage 3–4 (advanced disease progression). Baseline characteristics were balanced between groups except for age, occupation, WHO stage, and weight.

Clinical records were abstracted for 664 (85%) participants who attended their original clinic at 6 months and 580 (75%) at 12 months. Due in part to variable appointment attendance, study staff conducted 461 (59%) 6-month questionnaires and 453 (58%) 12-month questionnaires. Median (IQR) follow-up times were 7.1 (6.8–7.8) months and 13.0 (12.3–13.8) months for clinical abstraction, and 7.4 (7.0–8.2) months and 13.6 (12.9–15.0) months for

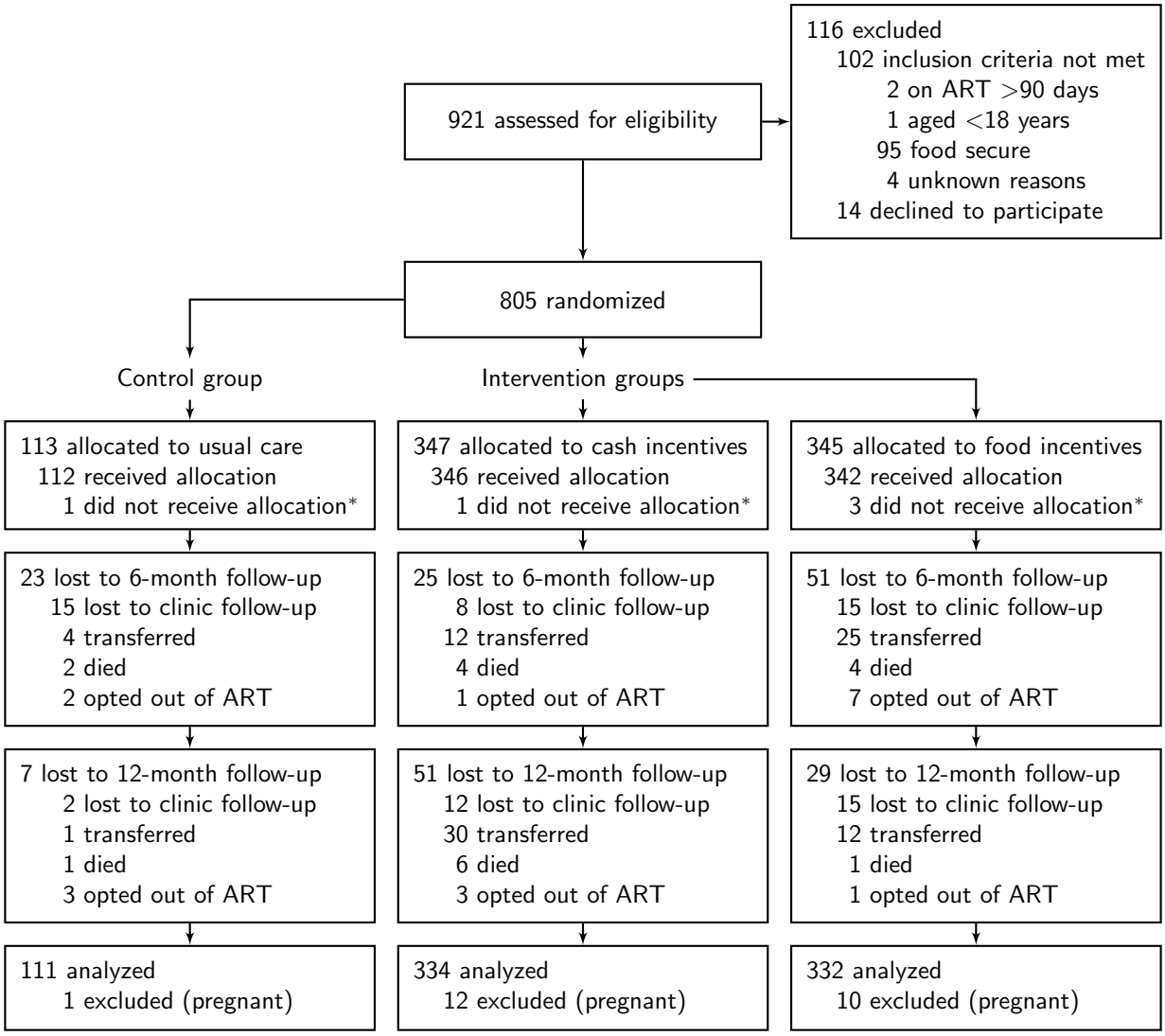

Figure 1.1: Trial profile, Tanzania, 2013-2015

*Died, transferred to another facility, or opted out before the first scheduled follow-up visit or missing all medical records.

Table 1.1: Baseline characteristics and outcome values of the modified intention-to-treat population, Tanzania, 2013-2015

			Intervention	
	Overall (n=777)*	Control (n=111)	Cash (n=334)	Food (n=332)
Sociodemographic Characteristics				
Age (years)	36.9 (10.3)	34.9 (9.3)	36.8 (10.0)	37.8 (10.8)
Female	486 (62.6%)	72 (64.9%)	206 (61.7%)	208 (62.7%)
Primary language is Swahili	477 (61.4%)	79 (71.2%)	199 (59.6%)	199 (59.9%)
No formal education	188 (24.6%)	23 (20.7%)	79 (24.2%)	86 (26.3%)
Farmer	400 (51.5%)	47 (42.3%)	189 (56.6%)	164 (49.4%)
Married or with partner	350 (45.1%)	50 (45.1%)	152 (45.5%)	148 (44.6%)
Head of household	484 (62.3%)	68 (61.3%)	204 (61.1%)	212 (63.9%)
Household size (members)	3.7 (2.1)	3.4 (1.8)	3.7 (2.1)	3.8 (2.1)
Clinic travel time (minutes)	46.6 (39.8)	40.4 (35.4)	46.5 (39.4)	48.8 (41.4)
Clinic travel cost (TZS)	1465 (2260)	1381 (2064)	1376 (2261)	1583 (2323)
Asset index (1-4)	2.5 (1.1)	2.6 (1.1)	2.5 (1.1)	2.5 (1.1)
Enrolled during lean season†	166 (21.4%)	27 (24.3%)	67 (20.1%)	72 (21.7%)
Clinical Characteristics				
Time on ART (days)	27.9 (25.5)	27.4 (25.8)	28.0 (25.6)	27.9 (25.4)
CD4 cell count (cells/μL)	203.7 (140.9)	214.5 (157.8)	199.1 (145.9	204.8 (129.8)
WHO clinical stage 3-4	451 (58.2%)	56 (50.5%)	214 (64.5%)	181 (54.5%)
Baseline Outcome Values				
Food Security				
HHS severe	323 (41.6%)	41 (36.9%)	138 (41.3%)	144 (43.4%)
HFIAS (0-27)	15.9 (5.2)	15.7 (5.2)	16.1 (5.1)	15.8 (5.2)
IDDS (0-9)	5.3 (0.7)	5.2 (0.8)	5.3 (0.7)	5.3 (0.7)
Nutritional Status				
BMI (kg/m^2)	21.4 (3.5)	21.7 (3.3)	21.2 (3.5)	21.5 (3.5)
BMI <18.5	122 (16.2%)	12 (11.0%)	56 (17.3%)	54 (16.9%)
Weight (kg)	56.3 (9.3)	58.2 (10.2)	55.5 (8.6)	56.5 (9.6)
Livelihood				
Currently working	454 (58.4%)	72 (64.9%)	194 (58.1%)	188 (55.6%)
Functional limitation‡	434 (55.9%)	64 (57.7%)	190 (56.9%)	180 (54.2%)

Data are mean (SD) or n (%). TZS, Tanzanian Shillings; WHO, World Health Organization; HHS, Household Hunger Scale; HFIAS, Household Food Insecurity Access Scale; IDDS, Individual Dietary Diversity Scale; BMI, body-mass index. *Of 805 food-insecure adults ART initiates randomized, 5 who did not receive the allocated intervention and 23 women who were pregnant at baseline were excluded from this analysis. Number of patients missing data for a particular variable: CD4 cell count: n=153. Body-mass index: n=24. All other variables: n<10. †September through January, during which time the "lean season" of widespread food insecurity typically occurs before the main harvest in this region. ‡Inability to do work or housework in the past year due to illness.

questionnaires; timing did not differ by study arm.

Participants in the control group were more commonly missing all follow-up measures (20.7%) compared to cash (8.4%) and food participants (16.0%), reflecting the previously demonstrated effectiveness of incentives at increasing retention in care. Additional predictors of censoring are shown in Table A.1. Higher baseline food insecurity (HFIAS) and lower asset

index predicted censoring in the control group only, suggesting that the interventions were more effective than the standard of care at retaining particularly disadvantaged participants in clinic-based care. For these reasons, the statistical analysis included inverse probability of censoring weights in an effort to address potential bias due to missing data.

Within-group temporal changes

All three study arms experienced within-group improvements in food security, nutritional status, and labor force participation from baseline to 6 and 12 months (Table 1.2).

Baseline to 6 months

In the primary weighted analysis, overall severe food insecurity (from HHS) declined from 38.2% at baseline to 13.0% at 6 months. Within the cash and food groups, severe HHS declined by 31.4 (95% CI: -38.9, -23.9) and 30.3 (-37.7, -22.9) percentage points (pp) respectively from baseline to 6 months. Within the control group, the proportion with severe HHS was similar from baseline to 6 months [-7.1 pp (-22.3, 8.2)].

Food access (HFIAS) improved within all groups from baseline to 6 months [Comparison: -4.1 (95% CI: -6.5, -1.7); Cash: -6.0 (-7.2, -4.9); Food: -5.6 (-6.7, -4.5)], along with increases in BMI [Comparison: 0.91 (0.57, 1.25); Cash: 0.93 (0.73, 1.14); Food: 1.11 (0.89, 1.32)], weight [Comparison: 2.3 kg (1.4, 3.2); Cash: 2.4 kg (1.9, 2.9); Food: 2.8 kg (2.3, 3.4)], and the proportion working [Comparison: 19.7 pp (5.4, 33.9); Cash: 14.9 pp (7.2, 22.6); Food: 19.1 pp (10.5, 27.6)]. There was no change in dietary diversity (IDDS) within any group from baseline to 6 months.

Baseline to 12 months

Within-group improvements from baseline in severe HHS, HFIAS, BMI, weight, and the proportion working were evident for all three study groups at 12 months. Functional limitation also decreased within the intervention groups only from baseline to 12 months [Cash: -27.6 pp (95% CI: -37.6, -17.7); Food: -24.8 pp (-34.0, -15.6)]. A slight improvement in IDDS was observed within the food group from baseline to 12 months [0.33 (0.16, 0.50)].

Average treatment effects

While all groups experienced temporal improvements from baseline to 6 months, compared to the standard of care the decline in severe food insecurity was 24.3 pp greater in the cash group (95% CI: -45.0, -3.5; p=0.015) and 23.3 pp greater in the food group (95% CI: -43.8, -2.7; p=0.020; Table 1.2; Figure 1.2). When directly compared, cash and food assistance had similar reductions in severe food insecurity. There were no between-group differences in the changes from baseline for food access, dietary diversity, weight, BMI, or work status over six months.

Table 1.2: Summary of the effects of cash and food incentives on food security, nutritional status, and livelihoods among HIV-infected adults, Tanzania, 2014-2016

		Mean Difference* from Baseline (95% CI)			Difference-in-Differences ATE† (95% CI)		
	N‡	Control (n=111)	Cash (n=334)	Food (n=332)	Cash vs. Control	Food vs. Control	Cash vs. Food
6 Months							
Food Security							
HHS severe	430	-7.1 (-22.3, 8.2)	-31.4 (-38.9, -23.9)	-30.3 (-37.7, -22.9)	-24.3 (-45.0, -3.5)	-23.3 (-43.8, -2.7)	-1.0 (-14.0, 12.0)
HFIAS (0-27)	429	-4.10 (-6.54, -1.66)	-6.03 (-7.18, -4.88)	-5.58 (-6.70, -4.45)	-1.93 (-5.22, 1.36)	-1.48 (-4.74, 1.79)	-0.45 (-2.42, 1.51)
IDDS (0-9)	458	0.08 (-0.25, 0.40)	0.06 (-0.08, 0.20)	0.09 (-0.05, 0.22)	-0.02 (-0.45, 0.41)	0.01 (-0.42, 0.44)	-0.03 (-0.26, 0.21)
Nutritional Status							
BMI (kg/m^2)	640	0.91 (0.57, 1.25)	0.93 (0.73, 1.14)	1.11 (0.89, 1.32)	0.02 (-0.46, 0.51)	0.20 (-0.29, 0.69)	-0.18 (-0.54, 0.19)
Weight (kg)	657	2.31 (1.39, 3.23)	2.40 (1.90, 2.91)	2.84 (2.30, 3.37)	0.09 (-1.19, 1.37)	0.53 (-0.77, 1.83)	-0.44 (-1.34, 0.46)
Livelihood							
Currently working	457	19.7 (5.4, 33.9)	14.9 (7.2, 22.6)	19.1 (10.5, 27.6)	-4.8 (-24.7, 15.1)	-0.6 (-21.0, 19.7)	-4.1 (-18.2, 10.0)
12 Months							
Food Security							
HHS severe	451	-36.2 (-49.6, -22.8)	-33.2 (-40.8, -25.6)	-36.0 (-43.8, -28.3)	3.0 (-15.9, 22.0)	0.2 (-18.7, 19.1)	2.8 (-10.5, 16.2)
HFIAS (0-27)	451	-7.26 (-9.29, -5.24)	-6.77 (-7.82, -5.71)	-5.96 (-6.98, -4.93)	0.50 (-2.31, 3.30)	1.31 (-1.47, 4.08)	-0.81 (-2.59, 0.97)
IDDS (0-9)	451	0.21 (0.00, 0.42)	0.11 (-0.04, 0.25)	0.33 (0.16, 0.50)	-0.10 (-0.42, 0.21)	0.12 (-0.21, 0.45)	-0.22 (-0.49, 0.04)
Nutritional Status							
BMI (kg/m^2)	554	1.21 (0.79, 1.63)	1.50 (1.15, 1.85)	1.38 (1.08, 1.67)	0.28 (-0.38, 0.95)	0.16 (-0.47, 0.79)	0.12 (-0.44, 0.68)
Weight (kg)	567	3.05 (1.95, 4.15)	3.85 (3.01, 4.70)	3.66 (2.91, 4.42)	0.80 (-0.89, 2.50)	0.61 (-1.02, 2.24)	0.19 (-1.19, 1.57)
Livelihood							
Currently working	447	25.7 (11.4, 40.0)	19.8 (11.6, 28.1)	25.2 (17.4, 33.0)	-5.9 (-26.0, 14.2)	-0.6 (-20.5, 19.4)	-5.4 (-19.2, 8.5)
Functional limitation	345	-18.0 (-40.6, 4.6)	-27.6 (-37.6, -17.7)	-24.8 (-34.0, -15.6)	-9.6 (-39.9, 20.6)	-6.8 (-36.8, 23.2)	-2.8 (-19.6, 13.9)

Data are modified intention-to-treat estimates (excluding 23 pregnant women and 5 participants who did not receive allocated intervention) from generalized estimating equation (GEE) models: with Gaussian distribution and identity link; using Bonferroni's correction for multiple comparisons; adjusted for clinic, baseline imbalances [age, occupation, WHO stage, and weight (except for weight and BMI models)], and prognostic factors (sex, education, head of household, household size, asset index, and lean season); and weighted with inverse probability of censoring weights estimated by treatment group, baseline characteristics, baseline values for HHS severe, HFIAS, IDDS, weight, currently working, and functional limitation, and 0-6 month or 0-12 month MPR$\geq$95%. Separate models were estimated for the change from baseline to 6 months and the change from baseline to 12 months due to non-monotone missingness, whereby some participants were observed at 12 months but not 6 months and vice versa. HHS, Household Hunger Scale; HFIAS, Household Food Insecurity Access Scale; IDDS, Individual Dietary Diversity Scale; BMI, body-mass index. *Within-group change from baseline in percentage point or continuous value at 6 and 12 months. †Between-group difference in the change from baseline in percentage point or continuous value at 6 and 12 months. ‡Number of subjects with fully observed baseline covariates (missing n=7) and the outcome observed at the specified follow-up time (6 or 12 months) out of 777 total subjects.

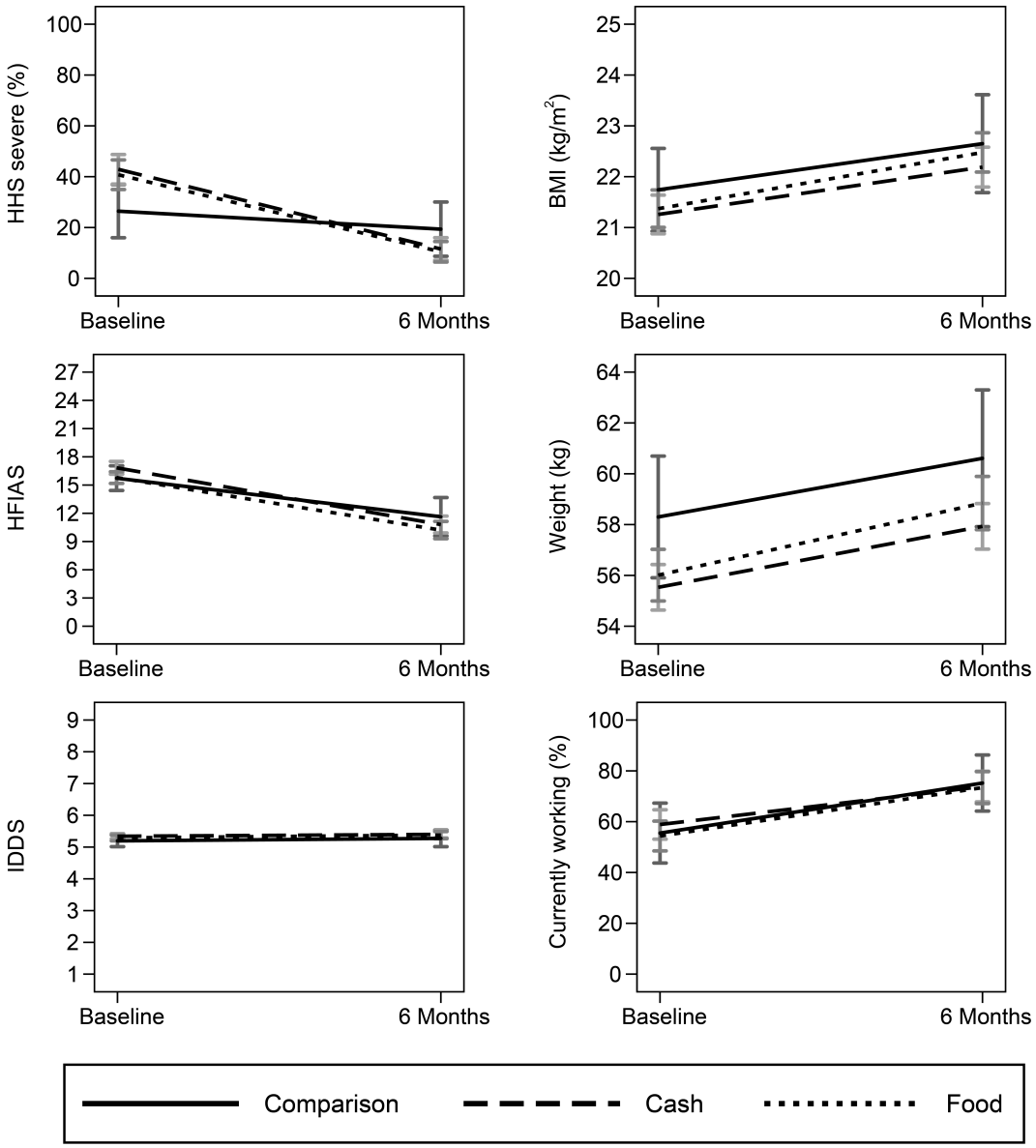

Figure 1.2: Changes in food insecurity, nutritional status, and work status among food-insecure antiretroviral therapy initiates after 6 months of standard HIV services alone or in combination with cash or food incentives, Tanzania, 2014-2016

From baseline to 12 months, although within-group temporal improvements from baseline persisted, differences in severe food insecurity between study groups were no longer observed. No between-group effects were evident for food access, dietary diversity, weight, work status, or functional limitation over 12 months.

In sensitivity analyses, results did not substantially differ when including women pregnant at baseline (Table A.3) or additionally excluding incident pregnancies (n=12), without adjustment for covariates (Table A.4), or using stabilized weights. Effects on severe food insecurity at 6 months were somewhat attenuated when excluding adherence (MPR≥95%) from the weights [cash vs. control: -21.9 (-43.7, -0.0); food vs. control: -21.0 (-43.0, 0.9)], due to the strong predictive value of adherence for both censoring (Table A.1) and food insecurity (6-month chi-square p=0.029). There were no between-group differences for any outcomes in unweighted complete case analyses (Table A.5). However, this latter approach does not account for potential bias arising from differential attrition by study group.

1.4 Discussion

A decade of research has documented the bi-directional links between food insecurity and HIV,[9, 10, 20, 21] leading to recommendations that interventions to mitigate food insecurity might improve treatment adherence.[25, 26] The parent analysis of the current study supported this hypothesis, demonstrating that short-term conditional cash and food assistance improves ART possession and retention in HIV services among food-insecure adults initiating treatment in Shinyanga, Tanzania.[28] The present analysis sought to understand potential pathways of impact by assessing whether incentives also improved food security and nutritional status, which were hypothesized *a priori* and shown in qualitative findings to be mediators of improved adherence in this trial.[55, 69] The findings showed that although all groups' food security, nutritional status, and work status improved from baseline to 6 months, the reduction in severe food insecurity was greater among participants assigned to cash or food assistance compared to the standard of care. Neither cash nor food enhanced the temporal improvements in food access, nutritional status, or work status which all groups experienced after six months on ART. At 12 months—six months after the intervention ceased—temporal improvements from baseline persisted within each group, with no between-group differences in food security, nutritional status, or labor force participation. These results may suggest that alleviating severe short-term food insecurity is a plausible explanation for some of the positive effects on retention and adherence.

Several observational or quasi-experimental studies of food assistance for people living with HIV have also demonstrated improvements in adherence and retention, however these studies yielded mixed results on food security and nutritional status.[29–33, 37] The lack of randomization in previous studies precludes inference about whether the intervention caused the observed outcomes. Inconsistencies may also derive from differences in sample size and char-

acteristics, attrition, intervention timing in relation to starting ART, follow-up time, and transfer sizes. For example, a study in Haiti with larger food basket sizes observed improvements in food security and BMI,[30] whereas the finding herein that cash and food transfers did not have an added effect on nutritional status is consistent with the three previous food assistance studies conducted in sub-Saharan Africa (none of which examined food security).[29, 31, 32] While the transfers in the present study appear effective for alleviating severe short-term household food insecurity, the lack of corresponding effects on individual nutritional status is understandable given that the basket was designed to supplement household consumption of local foods (as opposed to therapeutic treatment of undernutrition); both the basket and food purchased with cash were likely shared among household members, with little resultant increase in individual caloric intake.

It is important to emphasize that food security, nutritional status, and engagement in livelihood-generating activities improved within all groups over time, including the standard of care. Such improvements have been observed in other studies and attributed to the benefits of ART on physical health, in turn enabling participants to return to work and attain greater food security.[48, 49] Indeed, in the present study the overall prevalence of functional limitation declined from 53.9% at baseline to 29.3% at 12 months after adjusting for attrition. The improvements defy seasonal explanations, as a greater proportion of 6-month outcomes were measured during the "lean season" of widespread food insecurity among the general population (21% baseline vs. 67% 6-month interviews and 64% 6-month record abstraction, with no differences by arm) and improvements were maintained at 12 months. Furthermore, the models adjusted for enrollment during the lean season.

These findings add to a broader literature on the effects of cash and food transfers on food security and nutrition not only among HIV-infected populations.[39, 70–73] Cash and food transfers are provision incentives intended to meet basic needs and help to stabilize vulnerable households,[34] such as those starting ART who may be experiencing stress and economic shock due to stigma, illness, and loss of productivity.[35] Conditional transfers, such as those provided in this study, can operate via an income effect of increased economic wellbeing or via a price incentive whereby it is more "expensive" not to attend the clinic.[40] The finding that cash and food assistance appeared to alleviate severe short-term food insecurity to a greater extent than the standard of care may potentially represent an income effect, serving to increase adherence by overcoming the barrier of food insecurity at the critical time of treatment initiation. However—given the lack of effects on overall food security, nutritional status, or labor force participation—the transfers may be hypothesized to have operated primarily via the price incentive, improving ART adherence by increasing motivation and mitigating costs such as transportation, clinic fees, and time spent at the clinic. Via either mechanism, the improvement in ART adherence holds potential for future advances in patient wellbeing given a positive feedback cycle between adherence and food security.[48]

This study has important limitations. First, recruitment occurred during an era when ART

availability was limited to the sickest, before recent policy changes extended universal access to ART. However, these findings remain relevant given the high prevalence of food insecurity in the general population and the likelihood that many patients will continue initiating treatment at later disease stages. Next, the study was powered to detect effects on adherence, not marginal changes in food security and nutrition supplementary to the benefits of ART. Multiple comparisons increase the risk of over-interpreting a spurious result, a concern that was reduced by using the Bonferroni correction at the expense of precision. Substantial attrition from clinic-based care and study follow-up further limited power. Loss to follow-up—a pervasive problem in clinic-based studies—can also bias results if not properly addressed,[74] therefore inverse probability of censoring weights were applied.[62] This approach assumes that data are missing at random conditional on characteristics observed before censoring. However, observed patients may differ from censored patients with respect to missing outcome data, resulting in missing-not-at-random in which case results may still be biased. Under this scenario, whereby a relatively better-off control group is observed compared to those who were lost, the reported findings may underestimate the average treatment effects.

Despite the randomized design, imbalance in some baseline characteristics occurred by chance due to a relatively small sample size, especially in the control arm. This raises the possibility that the intervention groups had an increased probability of improvement due to worse baseline conditions. However, considering that all participants were highly disadvantaged at baseline, it is likely that any participant could have potentially benefited from the intervention had they been randomized to it. It is also possible that more disadvantaged participants would be less likely to benefit from treatment if they were unable to return to the clinic for subsequent appointments. Therefore, the magnitude and direction of any bias resulting from baseline imbalances is uncertain.

Lastly, outcomes were based on either self-report or record abstraction, each with limitations. Self-reported outcomes may be subject to influences such as social desirability. The use of record abstraction for anthropometry may have reduced the validity of weight and BMI measurements. It is anticipated that any misclassification would be non-differential by study arm and bias effects toward the null.

These limitations notwithstanding, this study has several strengths. The randomized design, including a referent standard-of-care group, provides an important contribution for evaluating the casual effects of cash and food assistance. The efforts to mitigate bias from attrition reinforce internal validity. Additionally, the inclusion of multiple measures of food insecurity and nutrition allows for a nuanced understanding of the effects on these outcomes. Finally, the follow-up to 12 months, six months after the incentives ended, provides some insight into the durability of effects.

In conclusion, these findings suggest that small cash and food transfers may mitigate the most severe form of food insecurity when provided at treatment initiation, a critical time of

habit formation amidst heightened household vulnerability to stress and economic shocks.[35] These effects may have facilitated the improvements in adherence and retention in care at 6 and 12 months as found in the primary analysis.[28] The implications of these findings for policy and practice suggest that even small cash or food transfers—when incorporated into HIV care—may serve as effective tools for addressing the HIV epidemic by improving ART adherence and the underlying barrier of food insecurity. Future studies are needed to better understand the optimal transfer amount to maximize both food security and adherence, and whether short-term cash and food assistance can sustain increased adherence and food security long after assistance ends.

Chapter 2

Biological effects & optimal implementation

Financial incentives to promote retention in care and viral suppression in adults with HIV initiating antiretroviral therapy in Tanzania: a three-arm randomized controlled trial

Summary

Background Financial incentives promote use of HIV services and might support adherence to the sustained antiretroviral therapy (ART) necessary for viral suppression, but few studies have assessed a biomarker of adherence or evaluated optimal implementation. This research sought to determine whether varying sized incentives for clinic attendance effected viral suppression among patients starting ART in Tanzania. **Methods** A three-arm parallel-group randomized controlled trial was conducted in Shinyanga region. At four health facilities, HIV-positive adult ($\geq$18 years) ART initiates ($\leq$30 days) were randomly allocated using a tablet-based application (1:1:1, stratified by site) to usual care (control group) or to additionally receive a cash incentive for monthly clinic attendance in one of two amounts: 10000 TZS (US $4.50) or 22500 TZS (US $10). Participants were masked to the existence of two incentive sizes. Incentives were provided for $\leq$6 months via mobile health technology (mHealth) that linked biometric attendance monitoring to automated mobile payments. The primary outcome of retention in care with viral suppression (<1000 copies/mL) at 6 months was evaluated using logistic regression. This trial is registered with ClinicalTrials.gov, NCT03351556. **Findings** From April 24, 2018 to December 14, 2018, 530 participants were randomized (184 control; 172 smaller incentive; 174 larger incentive); all were included in the primary intention-to-treat analysis. At 6 months, approximately 134 (73.0%) participants in the con-

trol group remained in care and achieved viral suppression, compared to 143 (82.9%) in the smaller incentive group [Risk Difference (RD)=9.8, 95% CI: 1.2–18.5] and 150 (86.1%) in the larger incentive group (RD=13.0, 95% CI: 4.5–21.5); a positive trend was identified between incentive size and viral suppression (p-trend=0.0032), although the incentive groups did not significantly differ (RD=3.2, 95% CI: -4.6–11.0). Adverse events included 18 deaths [7 (4%) control group, 11 (3%) intervention groups), none related to study participation. **Interpretation** Small financial incentives delivered using mHealth can improve retention in care and viral suppression among adults starting HIV treatment. While further research should investigate the durability of effects from short-term incentives, these findings strengthen the evidence for implementing financial incentives within standard HIV care.

2.1 Background

Viral suppression of HIV through sustained antiretroviral therapy (ART) provides significant individual health benefits and also prevents transmission.[4] Acting on this promise, global "treatment as prevention" efforts to end the HIV epidemic have markedly expanded access to ART.[75] However, substantial gaps remain in achieving population-level viral suppression, which can only be accomplished through testing, linkage to and retention in care, and continued individual adherence. Within East and Southern Africa—the region most affected by HIV—only 58% of people living with HIV attained viral suppression in 2018.[5] Attrition from care poses a key breakdown in the treatment cascade, especially in the first months after treatment initiation.[76] To address these challenges, increasing attention has focused on social determinants of health that may undermine retention and adherence, including poverty, food insecurity, stigma, social exclusion, discrimination, and other vulnerabilities commonly experienced by HIV-positive individuals.[77, 78] As one strategy to mitigate social and structural barriers limiting engagement with care, particularly in resource-constrained settings, recent reviews and UNAIDS guidelines have recommended implementing financial incentives linked to clinic attendance as part of a comprehensive HIV response.[78–80]

Financial incentives show promise for increasing viral suppression through pathways grounded in both traditional and behavioral economic theories.[81] First, incentives offset the price associated with clinic attendance, including transportation costs and opportunity costs such as time away from work, which impose substantial burdens for many individuals living with HIV. Depending on the size, incentives may also provide an income effect that partially alleviates poverty-related barriers to care. Insights from psychology suggest that incentives can counteract present bias, aiding individuals faced with day-to-day challenges of poverty to prioritize the future benefits of treatment.[82] Furthermore, even small incentives can provide a motivational "nudge" by signaling the importance of the incentivized behavior.[47]

Previous research based on process indicators, such as appointment attendance and medication dispensing, suggests that financial incentives linked to clinic attendance may improve

ART adherence in low- and middle-income countries (LMICs).[28, 83, 84] However, considerable gaps remain in understanding the viability of this strategy. Few studies of incentives have examined a biomarker for HIV viral suppression; of these, most focused on distinct sub-populations such as men who use drugs and pregnant women.[85, 86] Additionally, previous studies have rarely compared different incentive amounts, a key to understanding the mechanism for intervention impact and an important step toward identifying effective real-world implementation practices.[47] Moreover, complicated incentive delivery mechanisms used in previous studies—often requiring research staff to manually monitor eligibility and distribute payments by hand—may prove difficult to administer at scale. Thus, by evaluating two values of automated mobile payments provided upon clinic attendance, compared to a control group who received no incentives, this study sought to determine the effects of different sized financial incentives on viral suppression among adults starting HIV treatment in Tanzania.

2.2 Methods

Study design

A three-arm parallel-group randomized controlled trial was conducted at four HIV primary care facilities in Shinyanga region, Tanzania following procedures set forth in the study protocol. The Tanzania National Institute for Medical Research and the Committee for Protection of Human Subjects at the University of California, Berkeley provided ethics approval for this study. Here the study design and results are reported according to CONSORT 2010 guidelines.[87]

Participants

Study participants were recruited from the population of patients seeking care at the participating health facilities. Eligible individuals met the following inclusion criteria: 1) $\geq$18 years old; 2) living with HIV infection; and 3) initiated ART $\leq$30 days before. There were no formal exclusion criteria; however, patients known to be temporarily in-transit and those facing a language barrier were excluded. In coordination with facility staff, research assistants identified potential participants from facility records and then approached these patients upon attendance at the clinic to assess interest, confirm eligibility, and obtain written informed consent in Kiswahili.

Randomization and masking

Participants were individually randomized in a 1:1:1 allocation ratio to receive usual HIV care provided by the health facilities (control) or to additionally receive a monthly cash transfer for up to six months, conditional on visit attendance, in one of two amounts: 10000

TZS (about US $4.50) or 22500 TZS (about US $10.00). After completing informed consent, participant registration in the study's mobile health technology (mHealth) system, and a baseline interview to assess sociodemographic characteristics, research assistants conducted randomization using the mHealth system's custom application installed on tablet computers. The application sequentially allocated participants stratified within site using randomly permuted blocks of 30, which were generated by the application developers and concealed from research assistants and investigators. Neither participants nor research assistants were masked to intervention assignment, however participants were masked to the existence of two incentive sizes [at six months, only 6 of 457 (1.3%) participants surveyed indicated knowledge of both cash amounts under evaluation]. Clinic and laboratory staff (the latter of whom conducted viral load quantification at a separate facility) were not informed of intervention assignments.

Procedures

All participants received usual clinical care as provided by the health facilities. As per national and global guidelines in place at these facilities, patients starting ART visit the clinic on a monthly basis for at least six months for clinical assessment and monitoring (weight, vital signs, screening for opportunistic infections) and medication dispensing, including antiretroviral drugs to treat HIV.[88, 89] In alignment with this standard care model, participants in the two intervention arms could receive cash transfers up to once per month during the six consecutive months following enrollment, conditional on attending a clinic visit. Participants could receive the first cash transfer at a visit $\geq$6 days after study enrollment (to accommodate typical clinic scheduling of the first appointment one to two weeks after starting ART) and thereafter at any visits $\geq$26 days apart—regardless of appointment timeliness—up to a maximum of six transfers (totaling a potential of US $27-$60 depending on arm and visit attendance).

The incentives were intended to motivate clinic attendance, with the amounts chosen in consultation with local and national stakeholders and designed to partially counter the costs of transportation, food, and lost wages for a day spent at the clinic. A previous randomized trial in the region piloted the larger of the two incentive amounts and determined it to be safe, acceptable, and effective (compared to a control group receiving usual care) based on appointment attendance and medication dispensing process indicators.[28] This prior trial also evaluated the comparative effectiveness of cash incentive versus equivalently valued food baskets and found no statistically significant differences in retention or adherence, while cash was preferred by most study participants and logistically more feasible to distribute. The present study introduced the additional, smaller incentive amount to better understand the role of incentive size, including whether similar effectiveness could be achieved at a lower cost.

Attendance monitoring and cash transfer delivery was administered using the study's tablet-

based mHealth application, which linked biometric identification to an automated mobile payment system compatible with all mobile banking providers in Tanzania.[90] Participant fingerprints and mobile banking account details were registered in the mHealth system during study enrollment. Subsequent clinic attendance was logged in the mHealth system upon a fingerprint scan administered by a pharmacist or research assistant at the pharmacy. After the system verified payment eligibility, participants in the intervention groups immediately received their assigned amount in their mobile banking account (either 10000 TZS or 22500 TZS, plus transfer fees), including a notification on their mobile phone. Participants who did not have access to a mobile banking account received cash in hand from a research assistant.

Viral load testing occurred approximately six months after ART initiation as part of routine care, consistent with WHO and Tanzanian guidelines for monitoring HIV infection (after which adherent patients with suppressed viral load can transition to less frequent clinic attendance).[88, 89] Laboratory staff conducted blood specimen collection at the first visit after 5.5 months on ART, although in some cases the specimen was collected earlier or later, including repeat collection following a failed test. Whole blood samples (4ml) were transported to the hospital laboratory within 6 hours, centrifuged to retrieve plasma, and stored at -20°C. Samples were transported biweekly to a laboratory in Dar es Salaam for testing. The Cobas AmpliPrep (CAP)/Cobas TaqMan (CTM) 96 HIV-1 assay (Roche Molecular Systems, Branchburg, NJ) and Cobas 4800 were used for HIV viral load quantification. Results were typically available within two days of sample arrival at the laboratory.

Study staff conducted interviews and abstracted medical records at baseline and approximately six months. All interviews were conducted in Kiswahili and assessed socio-demographic characteristics and other self-reported attributes. Medical record abstraction included body weight, height, CD4 cell count, WHO Clinical Stage, and other routinely collected data. Additionally, at each visit a research assistant or pharmacist entered data into the mHealth system including medication type and quantity dispensed and next appointment date.

As retention in care was a key outcome of interest, no study-related efforts were made to contact participants who stopped attending the clinic until the six-month follow-up period was complete (while any routine tracing initiated by the clinic continued as usual). After six months, research assistants attempted to trace missing participants following PEPFAR guidelines, using phone calls, engagement with community health workers who conduct routine tracing, and triangulation with other facilities.[91] "Exhaustive" tracing efforts as defined by PEPFAR (three attempts using at least two tracing methods) were completed for all participants who stopped attending the clinic before the end of follow-up. If information suggested that a participant had transferred to another health facility, the new facility was contacted to verify whether the transfer occurred. Medical records for confirmed transfers were obtained from the new facility, including visit attendance and viral load test results if available. If no transfer was confirmed, the medical records from the original clinic were considered the last engagement with facility-based HIV care.

Outcomes

The primary outcome is HIV viral suppression, defined as the proportion of patients retained in ART care and virally suppressed (<1000 copies per mL, the WHO threshold for virologic failure[89]) at six months after starting ART. This outcome definition is consistent with global "treatment as prevention" strategies including the UNAIDS Fast-Track targets, which aim for at least 95% of people living with HIV to know their status, 95% of these to be retained in care, and 95% of these to be virally suppressed by 2030.[75] Following PEPFAR guidelines, patients considered not retained in ART care include those who died, disengaged from care or otherwise stopped ART, or had no evidence of facility-based care for ≥28 days after a missed appointment (i.e., the PEPFAR definition of lost to follow-up from facility-based care).[91] Thus, as recommended by PEPFAR, participants who could not be found after exhaustive tracing efforts (described above) were classified as not retained in care. Only viral load results for specimens collected from 5 through 7 months on ART were included in the analysis. Patients retained in care but without a valid viral load result in this window were considered to have a missing outcome.

Pre-specified secondary outcomes include the component measures of the primary viral suppression outcome—the proportion retained in care at six months and the proportion virally suppressed among only those retained in care—and mean appointment attendance, defined for each participant as the proportion of scheduled visits attended on-time (±4 days) over the 6-month follow-up period.[28] The mean number of visits attended during this period is also presented.

Statistical analysis

The trial was pre-registered at ClinicalTrials.gov (NCT03351556) and was overseen by a data safety monitoring committee. As part of the study design, the sample size was calculated as necessary to conduct a Cochran-Armitage linear trend test[92] between incentive size and the proportion achieving HIV viral suppression at six months. Assuming that 63% of participants in the control group would remain in care and achieve viral suppression at six months (based on adherence data from a previous study at the same clinics[28]), it was determined that 530 participants (150 per group given 15% loss to follow-up) would provide 80% power (two-sided α=0.05) to detect a trend if at least 70% of participants in the smaller incentive group and 78% in the larger incentive group achieved viral suppression.

Following the pre-specified analysis plan, first a test for a dose-response relationship between incentive size and 6-month viral suppression was done using a logistic regression model (corresponding to the Cochran-Armitage trend test), $logit(p) = a + b * x$, where p is the binomial proportion virally suppressed and x is the ordinal incentive amount (coded as 0, 10000, or 22500 TZS), against the null hypotheses of no trend ($H_0 : \beta = 0$ vs. $H_a : \beta \neq 0$) at α=0.05. Next, pairwise differences were calculated between groups for all outcomes by

modeling intervention arm as a three-level categorical variable, using logistic regression for binary outcomes and linear regression for appointment attendance. No adjustment was made for multiple comparisons. Only enrollment site was controlled for in the primary analyses, to account for stratified randomization.

Pre-specified secondary analyses included (1) additional adjustment for prognostic factors including age, sex, and baseline WHO clinical stage and (2) assessment of effect heterogeneity using Wald tests for interaction. To conserve statistical power, heterogeneity analyses compared the pooled incentive arms to the control. Pre-specified baseline variables examined for effect heterogeneity included sex, age, wealth index (relative within the study population; constructed using polychoric principal components analysis on the reported number of common household assets, similar to Demographic and Health Surveys[93]), and time since HIV diagnosis at ART initiation.

The primary intention-to-treat analysis included all randomized participants. As per the pre-specified analysis plan, multiple imputation[94] was used to estimate viral suppression status for a small minority who remained in care at six months but lacked a valid viral load result (i.e., missing values for the primary outcome, details described in Results). Note as a sensitivity analysis, complete-case estimates are also reported for viral suppression outcomes excluding participants who remained in care but lacked a viral load result. Multiple imputation was implemented with 20 iterations separately for each study arm using a logistic model, including the same pre-specified prognostic factors as in the secondary adjusted analysis (clinic, age, sex, and baseline WHO clinical stage). Results were combined according to Rubin's rules[94] using the "mi estimate" command in Stata.[95] All statistical analyses used Stata 14 (College Station, TX).

2.3 Results

Descriptive statistics

From April 24, 2018 to December 14, 2018, 530 participants were recruited and randomized; follow-up continued through June 20, 2019 and the primary analysis included all participants (Figure 2.1). Adverse events included seven deaths (4%) in the control group and 11 deaths in the intervention groups (3%), none related to study participation.

Participants were majority female with a median age of 35 years (Table 2.1). Nearly a quarter had no formal education and two in five had not worked in the past week, while over half were characterized as WHO Clinical Stage 1 (asymptomatic). All measured baseline characteristics were balanced between randomization arms.

During the six-month intervention period, participants received a total of 1631 payments upon visit attendance, mostly delivered through mobile banking (77.5%). Almost all par-

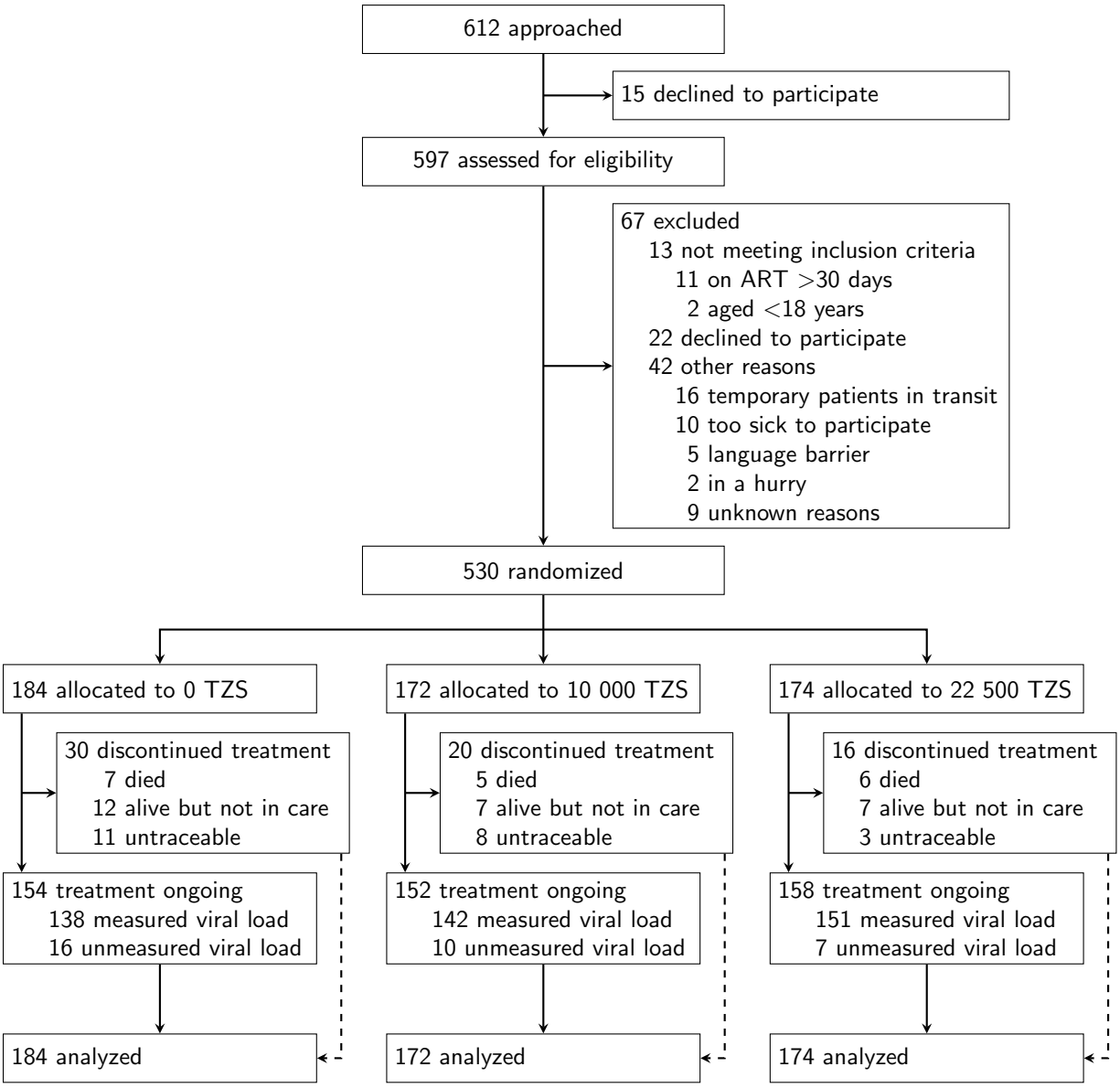

Figure 2.1: Trial profile, Tanzania, 2018-2019

Table 2.1: Baseline characteristics of the intention-to-treat population, HIV treatment initiates in Tanzania, 2018

	Total (n=530)	Control group (n=184)	Intervention groups	
			Smaller incentive* (n=172)	Larger incentive† (n=174)
Female	330 (62.3%)	116 (63.0%)	109 (63.4%)	105 (60.3%)
Age (years)	36.1 (10.2)	36.4 (10.3)	35.9 (9.0)	36.1 (11.3)
Primary language				
Swahili	244 (46.0%)	75 (40.8%)	88 (51.2%)	81 (46.6%)
Sukuma	264 (49.8%)	99 (53.8%)	78 (45.3%)	87 (50.0%)
Other	22 (4.2%)	10 (5.4%)	6 (3.5%)	6 (3.4%)
Educational attainment				
No formal education	115 (21.7%)	35 (19.0%)	43 (25.0%)	37 (21.3%)
Some primary	84 (15.8%)	31 (16.8%)	27 (15.7%)	26 (14.9%)
Primary completed	225 (48.1%)	96 (52.2%)	75 (43.6%)	84 (48.3%)
More than primary	77 (14.3%)	22 (12.0%)	27 (15.7%)	27 (15.5%)
Occupation				
Farming	114 (21.5%)	41 (22.3%)	30 (17.4%)	43 (24.7%)
Business	115 (21.7%)	42 (22.8%)	37 (21.5%)	36 (20.7%)
Other	249 (47.0%)	81 (44.0%)	85 (49.4%)	83 (47.7%)
Unemployed	52 (9.8%)	20 (10.9%)	20 (11.6%)	12 (6.9%)
Worked in the past week	309 (58.3%)	107 (58.2%)	93 (54.1%)	109 (62.6%)
Married or with partner	288 (54.3%)	100 (54.3%)	93 (54.1%)	95 (54.6%)
Head of household	401 (75.7%)	141 (76.6%)	127 (73.8%)	133 (76.4%)
Household size (members)	4 (2-6)	4 (2-6)	4 (2-6)	4 (2-6)
Wealth index				
Low	177 (33.4%)	58 (31.5%)	57 (33.1%)	62 (35.6%)
Middle	177 (33.4%)	68 (37.0%)	55 (32.0%)	54 (31.0%)
High	176 (33.2%)	58 (31.5%)	60 (34.9%)	58 (33.3%)
Health facility				
Referral hospital	42 (7.9%)	14 (7.6%)	14 (8.1%)	14 (8.0%)
Hospital	326 (61.5%)	114 (62.0%)	106 (61.6%)	106 (60.9%)
Health center	79 (14.9%)	27 (14.7%)	25 (14.5%)	27 (15.5%)
Dispensary	83 (15.7%)	29 (15.8%)	27 (15.7%)	27 (15.5%)
Time on ART (days)	10.6 (7.0)	10.3 (6.9)	10.0 (7.2)	11.4 (6.7)
Delay starting ART (days)	6 (0-9)	6 (1-8)	6 (0-9)	6 (0-9)
Weight (kg)	58.3 (11.0)	58.0 (11.3)	58.7 (10.6)	58.3 (11.2)
WHO Clinical Stage (1-4)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)	1.6 (0.7)
CD4 count (cells/μL)	369 (209-539)	352 (174-601)	394 (173-552)	414 (246-532)
Pregnant	18 (3.4%)	4 (2.2%)	7 (4.1%)	7 (4.0%)

Data are n (%), median (IQR), or mean (SD). ART=antiretroviral therapy. TZS=Tanzanian Shillings. All variables are fully observed except for CD4 cell count (n=229). *Smaller incentive group received 10 000 TZS. †Larger incentive group received 22 500 TZS.

ticipants in the incentive arms received at least one payment ([163 (95%) and 168 (97%) within the smaller and larger incentive arms, respectively]. On average, participants in the smaller incentive arm each received 4.6 total payments (SD=1.7) with 73% delivered through mobile banking, while participants in the larger incentive arm each received 4.8 (SD=1.6) total payments with 78% through mobile banking; these differences were not statistically significant.

At six months, overall 464 (87.6%) participants remained in care, including 28 confirmed transfers to another facility (Figure 2.1). Of 66 (12.5%) participants not in care, 18 had died, 26 were confirmed alive but not in care, and 22 could not be located after exhaustive tracing attempts (classified as not in care according to PEPFAR guidelines). A total of 33 participants [6.2%; 16 (8.7%) control, 10 (5.8%) smaller incentive, and 7 (4.0%) larger incentive; p=0.181] who remained in care lacked a valid viral load result because either a blood specimen was not drawn on time (n=22), the test failed (n=8), or the result was not returned from the laboratory (n=3); viral suppression was multiply imputed for these participants.

Average treatment effects

Following the pre-specified analysis plan, a positive dose-response relationship between incentive size and six-month viral suppression (OR=1.10 per 2500 TZS, 95% CI: 1.03–1.17, p-trend=0.0032) was first identified. In pairwise comparisons (Table 2.2 and Figure 2.2), relative to the control arm, a substantially greater proportion of participants remained in care and achieved viral suppression in both the smaller [82.9% vs. 73.0%, Risk Difference (RD)=9.8, 95% CI: 1.2–18.5] and larger incentive arms (86.1% vs. 73.0%, RD=13.0, 95% CI: 4.5–21.5). However, there was no statistically significant difference between incentive arms (RD=3.2, 95% CI: -4.6–11.0).

Similar patterns were observed for the secondary component outcomes of retention in care alone and viral suppression among those retained in care. Compared to the control arm, the larger incentive achieved significantly higher 6-month retention in care (90.8% vs. 83.7%, RD=7.1, 95% CI: 0.3–13.9) and viral suppression among those retained in care (94.9% vs. 87.1%, RD=7.8, 95% CI: 0.9–14.7); lesser improvements in these measures with the smaller incentive were not statistically significant (retention in care: 88.4% vs. 83.7%, RD=4.7, 95% CI: -2.5–11.8; viral suppression given retention in care: 93.8% vs. 87.1%, RD=6.7, 95% CI: -0.2–13.6). The mean proportion of appointments attended on-time substantially exceeded the control arm (80.0%) for both the smaller (87.4%, RD=7.4, 95% CI: 2.7–12.1) and larger incentive arms (90.5%, RD=10.5, 95% CI: 5.9–15.2). There were no statistically significant differences between incentive arms for any measures.

In secondary analyses, results were similar when additionally adjusting for prognostic factors (Table B.1) and in the complete-case sensitivity analysis (Table B.2).

Table 2.2: Summary of the effects of financial incentives on HIV viral suppression and retention on antiretroviral therapy at 6 months, Tanzania, 2018-2019

		Group estimate (SE)*			Between-group difference (95% CI)*		
Outcome at six months	N	0 TZS	10000 TZS	22500 TZS	10000 vs. 0	22500 vs. 0	22500 vs. 10000
Retained in care & virally suppressed†	530	73.0% (0.034)	82.9% (0.029)	86.1% (0.026)	9.8 (1.2, 18.5)	13.0 (4.5, 21.5)	3.2 (-4.6, 11.0)
Retained in care	530	83.7% (0.027)	88.4% (0.024)	90.8% (0.022)	4.7 (-2.5, 11.8)	7.1 (0.3, 13.9)	2.4 (-4.0, 8.8)
Virally suppressed‡	464	87.1% (0.030)	93.8% (0.021)	94.9% (0.018)	6.7 (-0.2, 13.6)	7.8 (0.9, 14.7)	1.1 (-4.4, 6.6)
Appointment attendance (%)§	530	80.0% (0.017)	87.4% (0.017)	90.5% (0.017)	7.4 (2.7, 12.1)	10.5 (5.9, 15.2)	3.1 (-1.7, 7.9)
Total number of visits attended	530	4.30 (0.129)	4.83 (0.133)	5.03 (0.133)	0.54 (0.17, 0.90)	0.73 (0.37, 0.11)	0.19 (-0.18, 0.56)

Data are estimates from generalized linear models adjusted for the clinic where randomization occurred. TZS=Tanzanian Shillings. ∗Viral suppression status was multiply imputed for 33 (6%) of 530 participants who remained in care but were missing a valid viral load result. †Primary outcome; the composite proportion of participants who remained in care at 6 months and had a viral load less than 1000 copies per mL. ‡Among those retained in care (n=464 overall). §The mean proportion of participants scheduled appointments over 6 months that were attended within 4 days of the scheduled date.

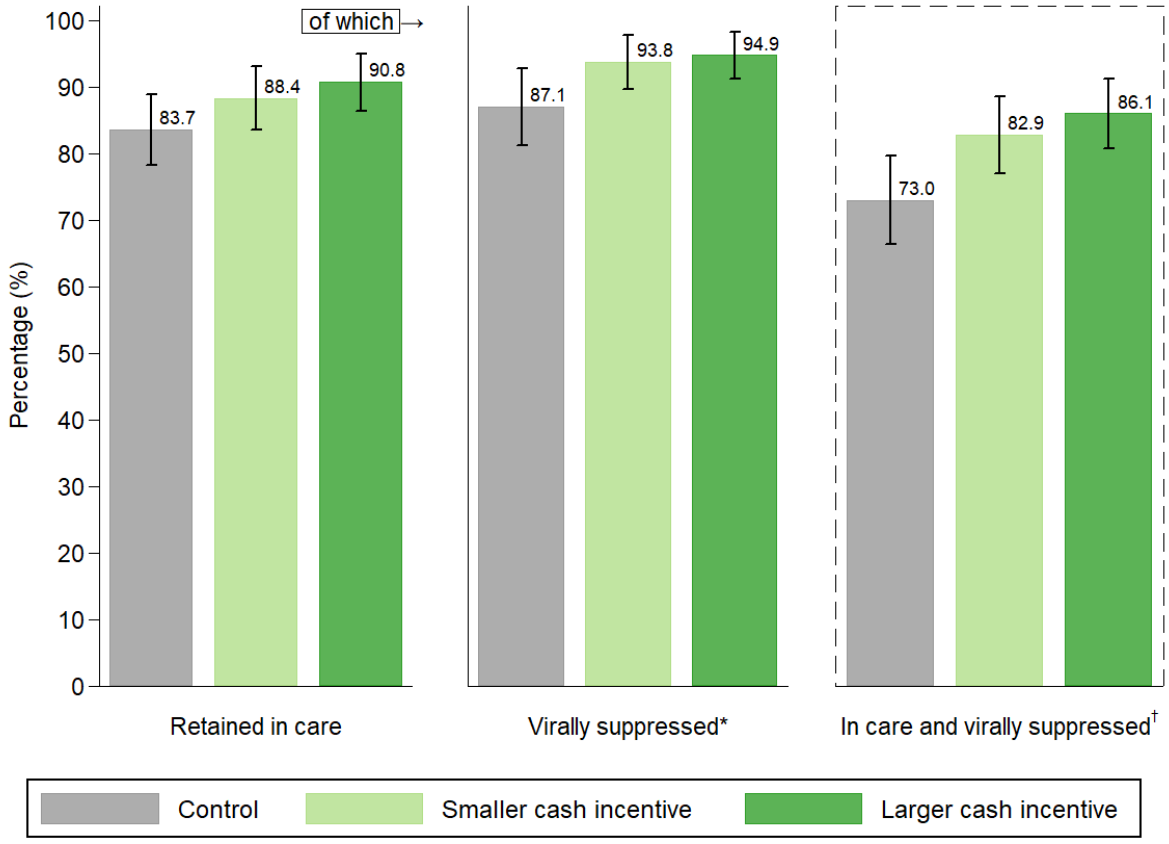

Figure 2.2: Retention in care and HIV viral suppression (<1000 copies per mL) at 6 months by intervention group, Tanzania, 2018-2019

Data are predictive marginal probabilities and 95% confidence intervals estimated from logistic regression models adjusted for clinic. *Of those retained in care at 6 months (N=464 out of total sample N=530). †Primary outcome; the composite proportion of patients who remained in care at six months and had a viral load <1000 copies per mL.

Effect heterogeneity

In heterogeneity analyses (Figure 2.3; Table B.3), disaggregating by relative wealth showed variation in the effectiveness of incentives (combined incentive arms compared to the control; p-interaction=0.068). In the lowest wealth tertile, incentives elevated the proportion retained in care and virally suppressed from 68.2% (control) to 87.1% (RD=18.9, 95% CI: 5.1–32.7), while in the highest wealth tertile incentives had no detectable effect as both groups achieved relatively high viral suppression (83.1% control vs. 83.6% cash, RD=0. 5, 95% CI: -11.9–12.9). Incentive effects on viral suppression did not substantially vary by sex, age, or timeliness of ART start after HIV-positive diagnosis (p-interaction>0.20 for all analyses).

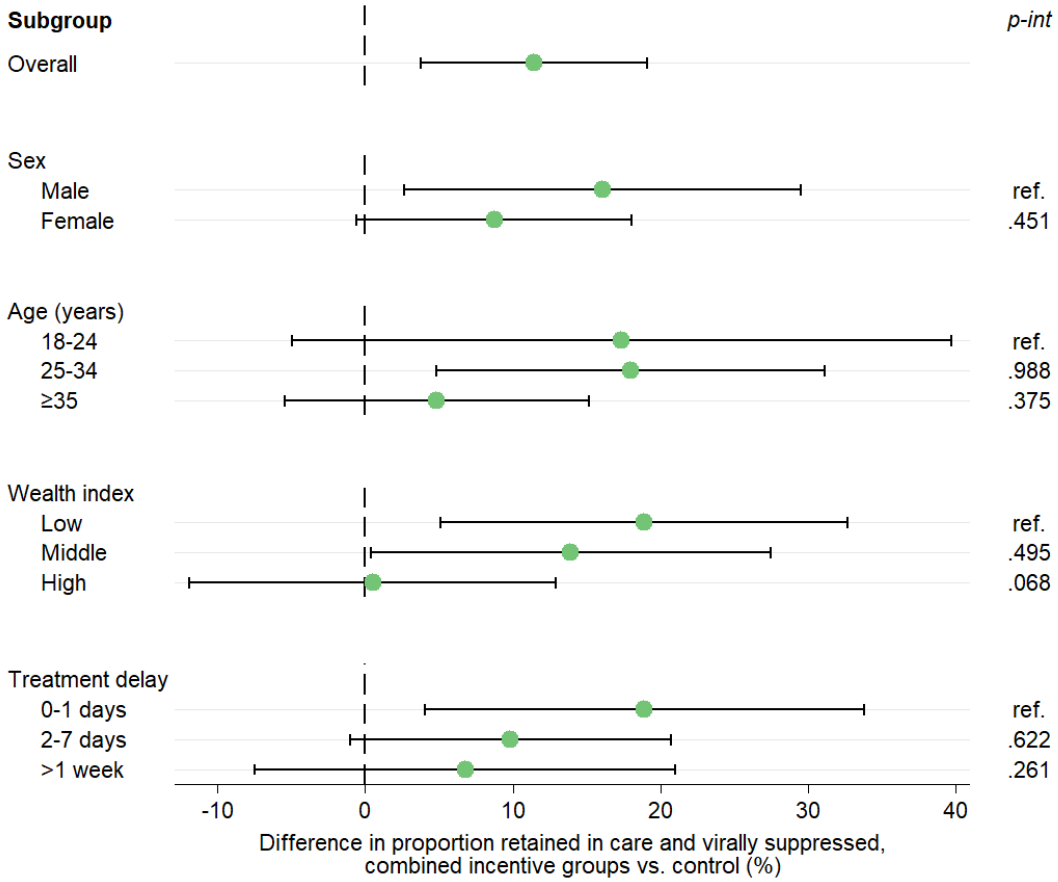

Figure 2.3: Effects of incentives (combined groups) on viral suppression within subgroups according to baseline characteristics, Tanzania, 2018-2019

Data are risk differences with 95% confidence intervals estimated from generalized linear models adjusted for clinic, comparing the combined financial incentive arms to the control arm who received no incentives. P-values for each interaction are shown.

2.4 Discussion

This randomized trial of 530 HIV-positive adults starting ART in Shinyanga, Tanzania found that small financial incentives improved the proportion of patients who remained in care and achieved viral suppression at six months by as much as 13 percentage points (with the larger of two incentive amounts tested), an 18% relative improvement over usual care. A positive trend between incentive amount and viral suppression was identified, while the study further demonstrated effectiveness of both tested amounts compared to the control. Incentives also bolstered retention in care alone, viral suppression among those retained in care, and appointment attendance. While direct comparison of incentive amounts showed no statistically significant differences for any outcome—which suggests possible diminishing returns from increasing incentive amount—the present study has limited power for this determination (as it was not designed for pairwise comparisons between arms). These findings contribute to a critical gap in understanding the effects of financial incentives on a biomarker of HIV treatment adherence. To our knowledge, this is the first randomized trial in a LMIC to evaluate the impact of financial incentives for treatment-seeking behavior on HIV viral suppression among a general population.

A recent review of conditional economic incentives for HIV treatment and prevention in LMICs found burgeoning evidence for positive effects on prevention outcomes and process indicators of treatment retention and adherence, but identified only three randomized trials that measured impacts on viral suppression.[81] The first of these studies, of 433 HIV-positive pregnant women in the Democratic Republic of the Congo, found that cash incentives delivered upon attending scheduled clinic visits and accepting proposed services (valued at US $5 for the first visit and escalating by $1 at each consecutive visit, up to a maximum total of $45 over six visits) resulted in higher retention in care at six weeks postpartum compared to a control group who received no incentives.[84] This trial evaluated viral suppression as a secondary outcome among the subset of participants who remained in care, finding no effect [66.1% intervention vs. 69.7% control virally suppressed among 174 (80.6%) and 158 (72.8%) respectively retained].[86] These findings translate to approximately 53.3% of the full intervention group retained in care and virally suppressed versus 50.7% of the control group, a risk difference of 2.6 percentage points. This smaller effect than in the current study may relate to differences in populations, study procedures, or treatment context.

The second study, of 120 HIV-positive men who use drugs in India, found that quarterly delivery of non-monetary vouchers redeemable for food or household goods (valued at US $4 for ART initiation, $4 for monthly visit attendance, and $8 for viral suppression at 6 or 12 months) increased linkage and retention in care compared to a control group who could receive similarly sized lottery prizes at quarterly visits, but did not improve viral suppression or CD4 cell count.[85] The authors outlined limitations including a small sample size and potentially restricted generalizability to other populations, and speculated that delayed payment for monthly visit attendance until the end of three-month intervals may

have diminished the potential salience of incentives for motivating daily adherence behaviors.

Lastly, a recent trial of adult patients on ART in Uganda incentivized the achievement of viral suppression at four timepoints, from 6 to 48 weeks, with escalating incentives (increasing from US $4 to $12.5) delivered after home-based viral load measurement; they too found no effect on viral suppression.[96] The authors noted possible explanations including high baseline viral suppression and frequent provision of viral load testing and counselling to all participants. Like the India-based study, they also suggested that incentives might have been too infrequent and not linked to interim behaviors on the pathway to viral suppression, including medication adherence. In summary, until now, no studies have investigated whether incentives delivered at the time of clinic attendance to a general adult population can improve viral suppression.

The present trial advances knowledge gained from previous studies in several important ways. This study was designed to evaluate a relatively simple implementation model feasible to administer in real-life clinical settings, including an automated mHealth system to regularly deliver monthly incentives through mobile banking. Incentives were provided on the 'soft' condition of clinic attendance, regardless of timeliness, to further simplify implementation and to avoid excluding disadvantaged patients facing the greatest obstacles to keeping appointments.[97] Payments were delivered in the pharmacy at the time of medication refill and thus directly tied to a component of adherence. This may partly explain the difference in effects on viral suppression between the present study and prior trials despite relatively similar incentive sizes across studies. Behavioral economic theory supports the notion that timing and salience matter for the success of health incentives.[47] In the present study, the effectiveness of both incentive amounts and the small non-significant difference between them—despite the larger value more than doubling the smaller one—suggests that these behavioral economic factors may have exerted an influence above and beyond the size of the incentive.

Additionally, the present study specifically targeted patients initiating ART, as numerous studies show that risk of attrition from care peaks in the first six months of treatment.[76] The rationale for this focus additionally considered the heightened clinical and economic vulnerability of patients at this time[35] and the potential to influence early habit formation for durable effects.[44] These findings suggest that financial incentives offered to adult ART initiates were indeed effective at least in the short term. While more work is needed to understand long term effects, preliminary data from the follow-up of a previous trial suggests that incentives for ART initiates do no harm and may have benefits even after withdrawn.[98] The present study also showed that poorer individuals may benefit most from incentives. However, attempting to target incentives based on wealth could complicate implementation and thereby hinder effectiveness, and again risk excluding individuals who stand to benefit, particularly given widespread poverty and challenges measuring wealth.

This study had important limitations. First, the trial was not powered to determine pairwise differences between groups (although these secondary comparisons were prespecified); it was primarily designed to evaluate the more efficient test for trend between incentive size and viral suppression. Therefore, given the imprecision in these pairwise measures of effect, the finding of no statistically significant difference between the incentive groups should be interpreted with caution. Moreover, the magnitude of effect may be viewed as only one of many important considerations when determining the optimal incentive size in a given setting, including availability of resources, stakeholder preferences, and the local economic context. Also, observed viral suppression surpassed expectations used in power calculations (based on an older study using a process-based adherence indicator), however the proportion virally suppressed among those in care in the control group matches current national data and significant improvements were still achieved.[5]

Additional limitations are countered by important strengths. While viral load results were missing for some participants who remained in care at six months, standard multiple imputation procedures were followed for these missing outcomes in order to include all participants in the primary analysis. This strategy sought to preserve the benefits of randomization and improve statistical power. Because these participants were few (6.2%), did not vary from others in terms of observable baseline characteristics apart from a small difference in mean age (which was included in the imputation model), and a complete-case sensitivity analysis yielded similar results, limited resultant bias is anticipated.

Separately, a small number of participants could not be located to confirm their status after exhaustive tracing and were thereby classified as not retained in care. While this protocol followed gold-standard PEPFAR indicator guidelines, misclassification may have occurred if patients had an undocumented facility transfer and achieved viral suppression. The proportion of untraceable participants among those not retained in care did not significantly vary by study arm, suggesting that potential misclassification may be non-differential by arm and would therefore bias results towards the null. As a final strength, findings from this study are supported by those from a previous trial of financial incentives for ART initiates in the same region, which found positive effects on medication possession ratio, an indicator of adherence.[28]

In conclusion, this study provides an important contribution to understanding the potential of financial incentives to achieve viral suppression in LMICs. While further research should investigate the durability of effects from short-term incentives such as those provided in this study, these findings strengthen the evidence for implementing small financial incentives within standard HIV care as part of a comprehensive strategy for epidemic control.

Chapter 3

Durability of effects

Durability of effects from short-term economic incentives for clinic attendance among adults with HIV in Tanzania: long-term follow-up of a randomized trial

Summary

Background Conditional economic incentives can improve medication adherence; however, any long-term harms or benefits from these predominantly short-term interventions remain largely unknown. This study evaluated outcomes 2 to 3 years after a 6-month incentive program. **Methods** Former participants were traced from a trial that randomized 800 food-insecure adults starting HIV treatment in Tanzania to receive usual care (control) or to additionally receive cash or food transfers ($11/mo) for ≤6 months, conditional on clinic attendance (ClinicalTrials.gov NCT01957917). The primary intention-to-treat analysis estimated 24- and 36-month marginal risk differences (RD) in retention in care and all-cause mortality comparing combined incentive arms to the control, with multiple imputation for missing outcomes. Mortality hazard ratios (HR) were also estimated from time-stratified Cox regression. **Findings** From March 3, 2018 to September 19, 2019, tracing and determination of 36-month care and mortality statuses was conducted for 737 (92%) and 700 (88%) participants, respectively. Overall, approximately 660 (83%) participants were in care at 36 months while 43 (5%) had died. There were no differences in retention at 24 months (86.5% vs. 84.4%, RD=2.1, 95% CI: -5.2, 9.3) or 36 months (83.3% vs. 77.8%, RD=5.6, 95% CI: -2.7, 13.8), nor in mortality at either timepoint. The intervention group had a lower rate of death during the first 18 months (HR=0.27, 95% CI: 0.10, 0.74; p-interaction=0.076); mortality was similar thereafter (18-36-month HR=1.13, 95% CI: 0.33, 3.79). **Interpretation** These findings confirm that incentives are a safe and effective tool to promote short-term adherence and potentially avert early deaths at the critical time of HIV treatment initiation. Complementary strategies are recommended to sustain lifelong adherence.

3.1 Background

Conditional economic incentives such as cash and in-kind transfers have shown success at improving health care utilization and health outcomes across a variety of domains, from maternal and child health to chronic disease management.[47] Well-known examples include comprehensive government anti-poverty programs, such as Mexico's conditional cash transfer program[3], which typically provide large, sustained incentives for engaging in various health and education services. Distinctly, a growing body of literature has evaluated discrete interventions that offer smaller, short-term incentives targeting specific outcomes, such as vaccination or facility delivery. These initiatives often seek to impact health through economic and psychological pathways.

One mechanism by which incentives might elicit behavior change involves providing "extrinsic" motivation, or an increased desire to do something to earn an external reward. An often cited worry with short-term incentives concerns the potential for crowding out free-choice "intrinsic" motivation, resulting in less willingness to engage in the activity once incentives end.[41] According to this hypothesis, incentives could prove to be harmful in the long run. However, others argue that data supporting the crowding out hypothesis are primarily from controlled experiments, often with university students, with little evidence founded on real-world settings.[43] An alternative hypothesis suggests that extrinsic rewards may *activate* intrinsic motivation and promote sustained habit formation.[44] Another possibility is that incentive effects gradually wane to zero after the intervention ends. Yet most studies do not measure outcomes beyond the end of the intervention period due to time and resource constraints, leaving uncertainty around the potential long-term harms or benefits of short-term incentives.

An increasingly common use of incentives focuses on medication adherence. Poor adherence to medication manifests as a global problem across conditions and diseases, threatening treatment success and contributing to increased healthcare costs.[99] Reviews of incentive strategies for medication adherence show short-term effectiveness across a range of outcomes, including substance abuse, tuberculosis, HIV, and stroke prevention.[100, 101] The rare examinations of long-term outcomes indicate diminishing adherence effects after discontinuing incentives, like other behavioral interventions, but no evidence of eventual harm.[101]

In the realm of HIV, medication adherence poses a critical challenge offering a high reward. Efficacious, widely available treatment for HIV with antiretroviral therapy (ART) enables individuals to lead long and healthy lives, while also inhibiting transmission and thereby promising an end to the HIV epidemic.[4] However, these benefits rely on lifelong adherence to ART, a difficult task especially considering the myriad social and economic barriers commonly faced by people living with HIV. Recent evidence demonstrates that short-term incentives can bolster HIV treatment adherence and viral suppression in low- and middle-income countries (LMICs), which shoulder the greatest burden of HIV.[102] Still, no studies

in LMICs have evaluated long-term harms or benefits of incentives for HIV treatment adherence.

To better understand the effectiveness of incentives for improving HIV treatment outcomes, this study sought to evaluate two- to three-year results from a previously conducted study of short-term cash and food incentives for HIV care in Tanzania. Compared to a control group that received usual care, the original randomized trial (2013-2016) found that both types of incentives significantly improved ART adherence during a 6-month incentive period at the start of HIV treatment, with smaller effects persisting 6 months after the incentives ended.[28] The present study followed up original study participants to evaluate long-term effects of the incentive program.

3.2 Methods

Study design

This study evaluated 24- and 36-month outcomes for a three-arm parallel-group randomized controlled trial that was conducted from 2013 to 2016 at three HIV primary care facilities in Shinyanga Region, Tanzania. Study procedures from the original trial have been previously described.[28, 55] The present follow-up study was pre-registered as an extension of the original trial (ClinicalTrials.gov, NCT03351556), and here the results are reported according to CONSORT 2010 guidelines.[103] The Tanzania National Institute for Medical Research and the Committee for Protection of Human Subjects at the University of California, Berkeley provided ethics approval.

Participants

Study participants in the original trial (Table 3.1) were recruited from the population seeking care at the three included health facilities. Eligible individuals met the following inclusion criteria: 1) $\geq$18 years old; 2) living with HIV infection; 3) initiated ART $\leq$90 days before; and 4) food insecure, according to the Household Hunger Scale[56]; participants provided written informed consent. The present study followed up with the same individuals who participated in the original trial. After tracing former participants, informed consent to participate in the follow-up study was obtained in written or verbal forms or waived (as described in Procedures below).

Randomization and masking

The original trial individually randomized participants in a 1:3:3 allocation ratio to receive usual HIV care provided by the health facilities (control) or to additionally receive a monthly economic incentive for up to 6 months, conditional on visit attendance, in one of two forms: a food basket (12kg maize meal, 3kg groundnuts, and 3kg beans) or an equivalently valued

cash transfer (22500 TZS, US $11). Non-blinded site-stratified randomization was conducted by research assistants using opaque sealed envelopes, which were assembled at UC Berkeley and ordered in randomly permuted blocks (7, 14, or 21) generated with Stata 12 (College Station, TX).

Table 3.1: Participant characteristics at baseline, HIV treatment initiates in Tanzania, 2013-2015

	Total (n=800)	Control (n=112)	Intervention (n=688)
Female	509 (63.6%)	73 (65.2%)	436 (63.4%)
Age (years)	35.0 (29.0-43.0)	33.0 (28.0-40.0)	35.0 (30.0-43.0)
Married or lives with partner	345 (43.1%)	49 (43.8%)	296 (43.0%)
Primary language is Swahili	489 (61.1%)	80 (71.4%)	409 (59.4%)
Educational attainment			
No formal education	194 (24.3%)	23 (20.5%)	171 (24.9%)
Some pre-/primary school	121 (15.1%)	16 (14.3%)	105 (15.3%)
Completed primary school	437 (54.6%)	61 (54.5%)	376 (54.7%)
Secondary school or more	48 (6.0%)	12 (10.7%)	36 (5.2%)
Occupation			
Farmer	405 (50.6%)	47 (42.0%)	358 (52.0%)
Business	105 (13.1%)	25 (22.3%)	80 (11.6%)
Other	181 (22.6%)	27 (24.1%)	154 (22.4%)
Unemployed	109 (13.6%)	13 (11.6%)	96 (14.0%)
Currently working	462 (57.8%)	72 (64.3%)	390 (56.7%)
Facility			
Referral Hospital	188 (23.5%)	26 (23.2%)	162 (23.5%)
Hospital	523 (65.4%)	73 (65.2%)	450 (65.4%)
Health Center	89 (11.1%)	13 (11.6%)	76 (11.0%)
Travel time to facility (minutes)	30.0 (20.0-60.0)	30.0 (20.0-60.0)	30.0 (20.0-60.0)
WHO clinical stage			
Stage 1	113 (14.1%)	14 (12.5%)	99 (14.4%)
Stage 2	232 (29.0%)	41 (36.6%)	191 (27.8%)
Stage 3	411 (51.4%)	47 (42.0%)	364 (52.9%)
Stage 4	44 (5.5%)	10 (8.9%)	34 (4.9%)
Time on ART (days)	14.0 (12.0-44.0)	14.0 (0.0-44.0)	14.0 (13.0-44.0)

Data are n (%) or median (IQR). ART=antiretroviral therapy. WHO=World Health Organization.

Procedures

All participants received standard clinical care as provided by the health facilities, both during the six-month intervention and thereafter. Following national guidelines for individuals starting ART, participants were directed to visit the clinic on a monthly basis for clinical evaluation and medication dispensing, including antiretroviral drugs (ARVs) to treat HIV.[57] Along with this usual care, participants in the two intervention arms could receive food or cash transfers up to once per month during the six consecutive months following trial enrollment, conditional on timely attendance at a scheduled clinic visit (within ± 4 days). Research assistants monitored appointment attendance and distributed food baskets

and cash transfers on the same two days per month. Participants could receive up to six transfers, for a maximum total value of 135000 TZS (US $66).

There were no study-related efforts to contact participants who stopped attending the clinic during the original 12 month trial (while any routine tracing initiated by the clinic continued as usual; in the original analysis,[28] participants with a documented transfer were censored while the remainder who stopped attending the study facilities were considered not in care). For the present follow-up study, after 36 months had elapsed since original enrollment in the trial, research assistants worked with clinic staff to trace former participants, re-enroll them in the study, and conduct data collection.

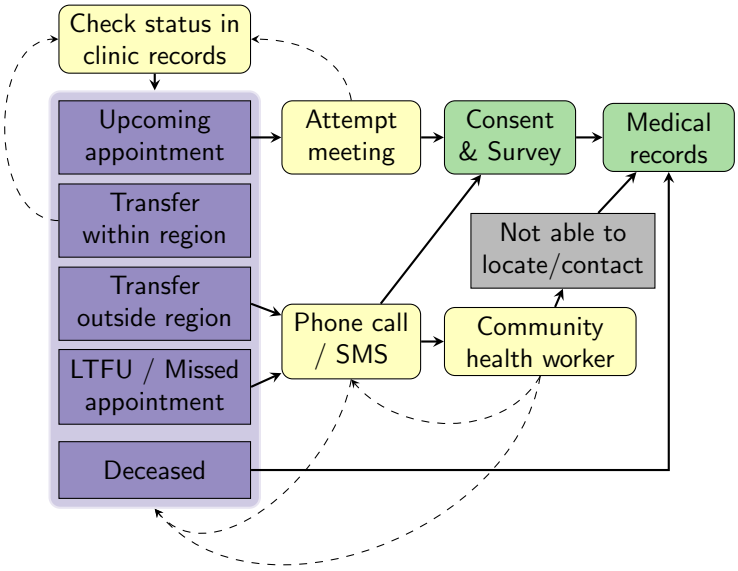

Figure 3.1: Tracing strategy

Tracing procedures followed PEPFAR guidelines,[91] using phone calls, engagement with community health workers who conduct routine tracing, and triangulation with other facilities (Figure 3.1). First, the last known status for each participant was abstracted from clinic records at the original three facilities. Individuals confirmed to be in care at the original facility or another facility within Shinyanga region were approached by research assistants during a scheduled clinic visit, after clinic staff obtained the individual's permission for study contact. If an individual's medical record specified an out-of-region transfer or that the most recent scheduled appointment was missed, clinic staff attempted to call or text; those who could not be reached by phone were referred to community health workers for tracing. Given successful tracing and agreement to be contacted by study staff, research assistants scheduled either an in-person meeting at a location preferred by the individual (home, community location, or clinic) or a phone call if the individual no longer lived within the region.

Efforts to trace each participant continued until successful location or the conclusion of "exhaustive" tracing efforts as defined by PEPFAR ($\geq$3 attempts using at least two tracing methods). After contacting former participants, research assistants confirmed each individual's identity and participation in the original trial, obtained consent to participate in the follow-up study, completed an interview, and abstracted all available medical records from facilities attended since starting ART. Written informed consent was obtained in person for contacted individuals who were still living within Shinyanga region; verbal consent was obtained over the phone for individuals who had moved out of the region; and a waiver of informed consent to access medical records applied to individuals found to be deceased or who could not be located after exhaustive tracing (as defined above).

All interviews were conducted in Kiswahili and collected information about experiences and preferences regarding HIV care along with socio-demographic characteristics. Clinical visit dates, appointment dates, medication dispensing, WHO Clinical Stage, and other routinely collected HIV care data were abstracted from available medical records, including facility databases, paper-based records, and a card carried by individuals to all care encounters including temporary in-transit clinic visits.

Outcomes

The primary pre-specified outcome was retention in care, measured by clinic attendance records at 24 and 36 months after enrollment. Following PEPFAR guidelines,[91] individuals considered not retained in care included those who died, disengaged from care or otherwise stopped ART, or had no evidence of care for $\geq$90 days after a missed appointment as of 24 and 36 months (this 90-day definition of LTFU, used in the original trial analysis and other studies,[28, 104] was used instead of PEPFAR's updated 28-day definition in order to reduce any misclassification stemming from incomplete clinic attendance records). As recommended by PEPFAR, participants who could not be found after exhaustive tracing efforts were classified as not retained in care. However, retention in care was conservatively considered to be missing for former participants whose last known status indicated a transfer that could not be verified (i.e., complete medical records from the facility could not be accessed, primarily in the case of out-of-region facilities as these were not visited in-person).

All-cause mortality, a component of retention in care, was assessed as a secondary outcome at 24 and 36 months and used in a time-to-event analysis. Mortality status and date of death were obtained through medical records or contact with family members during tracing. While the study also intended to evaluate the medication possession ratio over 12-36 months, this was deemed infeasible due to incomplete medication dispensing records obtained at follow-up.

Statistical analysis

The target sample size for the original trial was calculated based on two objectives tied to 6-month ART adherence: a non-inferiority analysis to compare cash versus food incentives, and an effectiveness analysis comparing any incentives (combined cash and food groups) to usual care. For 80% power, the non-inferiority design required 339 participants in each incentive group, assuming 75% adherence in the food group, a non-inferiority limit of 10 percentage points for the cash group, one-sided alpha=0.025, and 15% loss to follow-up. The effectiveness of the combined incentive groups over usual care analysis required a control group of 110 participants for a minimum detectable effect of 15 percentage-points, assuming 60% adherence in the control group and alpha=0.05. The follow-up study applied this same approach, comparing the pooled incentive groups to the control group, to evaluate durability of effectiveness over usual care among all original study participants.

First, descriptive analyses were conducted regarding participant mobility and continuity of care over time, as crucial and often poorly understood factors in retention on ART. This included examining survey responses about moving and distance-related clinic preferences, assessing the proportions attending the original facility of ART initiation or new facilities at follow-up, and evaluating the median Euclidian distance between original facilities and transfer facilities attended at 36 months.

The primary analysis followed the same methods as in the pre-specified analysis of the original trial.[28, 55] An intention-to-treat analysis was conducted to evaluate the primary outcome of retention in care and the secondary outcome of mortality at 24 and 36 months. Using predicted probabilities from logistic regression models, outcomes were expressed as marginal mean differences between the combined incentive and control groups with 95% confidence intervals (CI).[105, 106] Only enrollment site was controlled for in the primary analyses to account for stratified randomization.

To evaluate changes in incentive effects after the end of the 6-month intervention period, longitudinal generalized estimating equation (GEE) models of retention and death were also fit, including terms for intervention arm, time indicators (6, 12, 24, and 36 months), clinic, and interaction between intervention arm and time. Similar to the primary analysis, the longitudinal models used the binomial distribution and logit link and were used to estimate and contrast marginal mean differences in predictive probabilities.

In secondary analyses, the primary logistic regression models were additionally adjusted for baseline characteristics including age, sex, and characteristics that were imbalanced at baseline of the original trial (WHO clinical stage, occupation, and language). Effect heterogeneity was also explored across the same subgroups as in an analysis of the original trial results[107] (sex, age, wealth index, and treatment delay between HIV diagnosis and ART initiation) with a Wald test of the interaction term at alpha=0.20, while expecting these analyses to be underpowered.

Lastly, the effect of incentives on time to all-cause mortality was examined. An unadjusted Kaplan-Meier plot stratified by study group and a Cox proportional hazards model were used to compare the relative mortality rates by group. The Cox model was adjusted for clinic, as in the primary analysis. A time period by arm interaction was also added after detecting evidence of proportional-hazards violation (Schoenfeld residuals p=0.006), using two equal 18-month time periods (0-18 months, 18-36 months) to satisfy the proportional-hazards assumption. As such, hazard ratios are reported by time interval.

The primary intention-to-treat analyses of effect estimates at 24 and 36 months included all randomized participants. Multiple imputation was used to account for missing retention in care and mortality for a minority of participants who were missing values for each outcome. Sequential multiple imputation was implemented with 20 iterations separately for intervention and control arms using logistic models, including the same fully-observed predictors used for this purpose in a similar trial (clinic, age, sex, and WHO clinical stage).[102] Parameter estimates were combined according to Rubin's rules.[94, 95] As a sensitivity analysis, complete-case estimates are also reported for all outcomes (excluding participants with missing data). For survival analyses, individuals missing 36-month mortality status were censored at the date last known to be alive. All statistical analyses were conducted using Stata 14 (College Station, TX).

3.3 Results

Descriptive findings

Between December 2, 2013 and July 22, 2015, the original trial recruited and randomized 805 individuals; 5 were immediately lost to follow-up and were excluded from both the original trial and the present analysis.[28] Follow-up to ascertain 24- and 36-month outcomes occurred between March 3, 2018 and September 19, 2019, with all 800 original participants [509 (64%) women] included in the primary analysis (Figure 3.2).

The follow-up study abstracted available medical records for all 800 participants and interviewed a total of 530 participants [348 (66%) women]. Most interviews [408 (77%)] were conducted at the original health facilities, along with 94 (18%) at another facility or location within Shinyanga region and 28 (5%) over the phone with participants who had relocated to another region. The median follow-up period at the time of the interview was 48 months [interquartile range (IQR): 43-52].

Participant responses indicated high mobility: one in three [162 (31%)] reported moving to a different place of residence since enrollment in the original trial. Additionally, a quarter of those in care at the time of the interview [135 of 521 (26%)] reported currently attending a facility other than the one nearest to their home, with the most commonly cited reasons including continuing care at the same facility where they started treatment [35 (26%)], fear

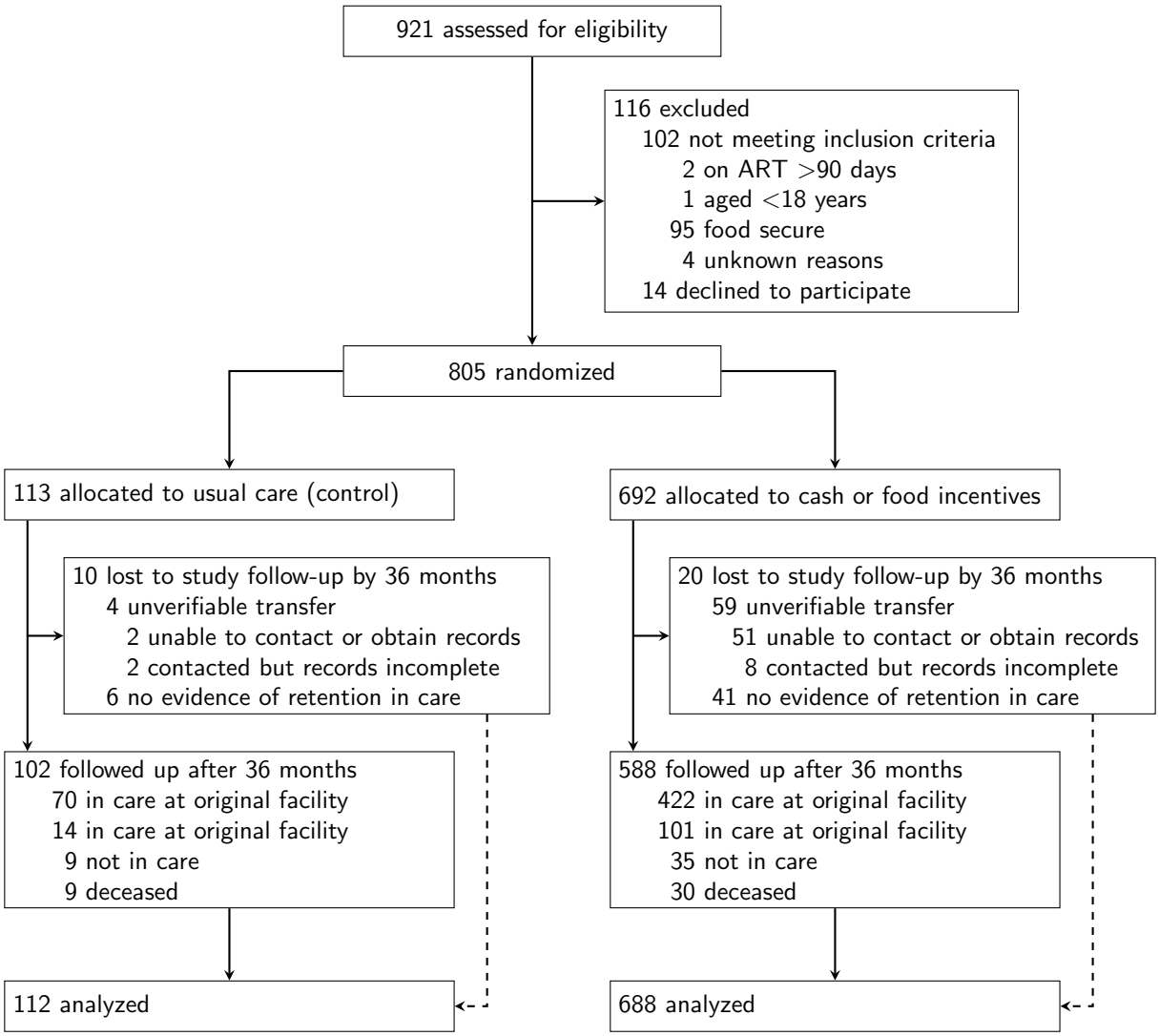

Figure 3.2: Trial profile, Tanzania, 2013-2018

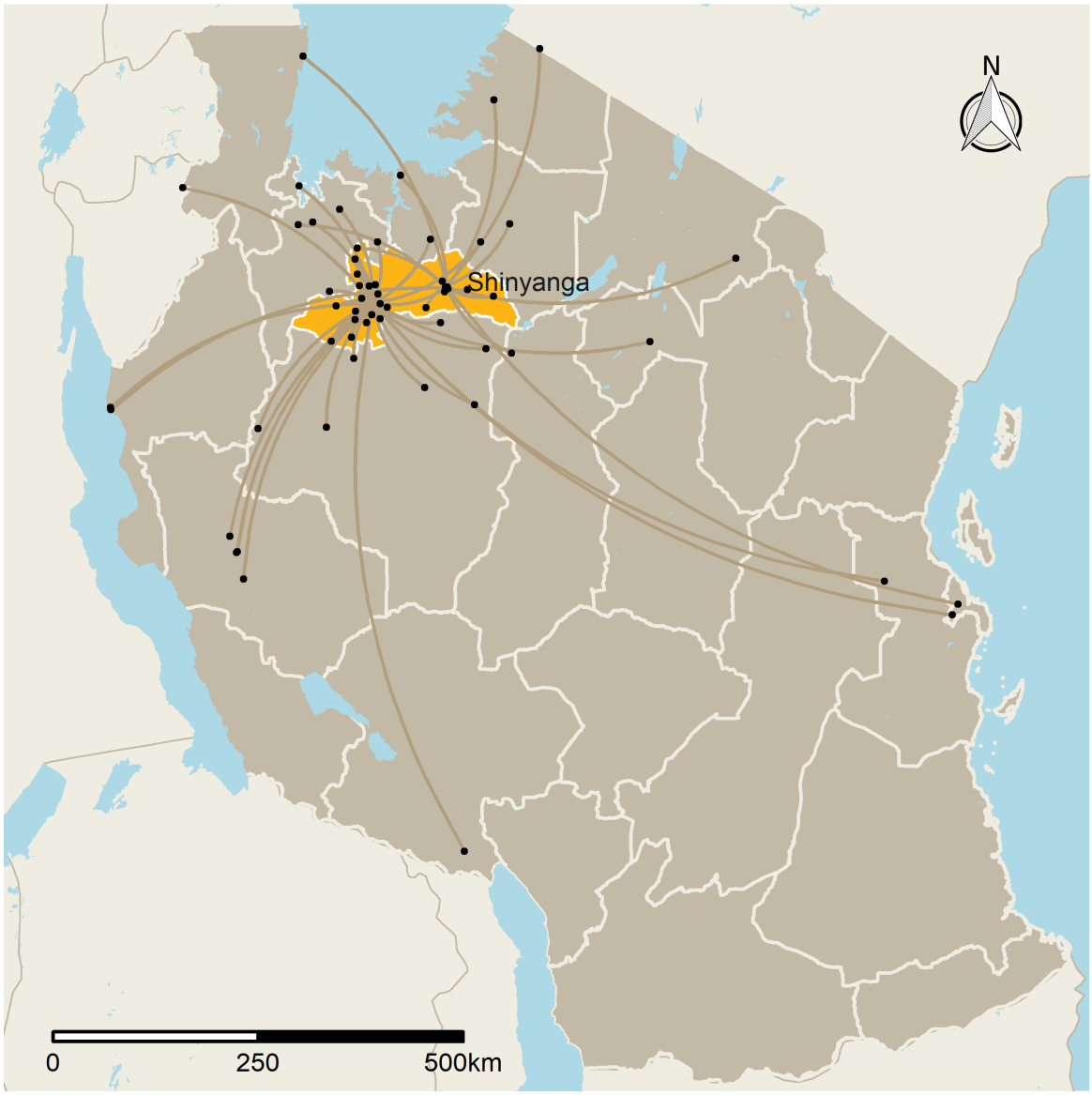

Figure 3.3: Locations where traced participants received HIV care at 36 months according to medical records, Tanzania, 2015-2018

of stigma or HIV status disclosure at their local facility [28 (21%)], and quality of services [16 (12%)].

According to clinical records at 24 and 36 months, respectively, 556 (70%) and 494 (62%) participants were engaged in care at the same health facility as at trial enrollment, with no significant differences between intervention and control groups. Receipt of care at another facility was verified for 84 participants (26 out-of-region) at 24 months and 115 participants (35 out-of-region) at 36 months. The median distance between the original facility and a 36-month transfer facility was 20 kilometers (IQR: 12-102, Figure 3.3). Records also indicated potential transfers for an additional 56 (7%) participants before 24 months and 63 (8%) before 36 months, however records could not be obtained to verify these transfers (due to of out-of-region or long past transfers); retention in care was therefore estimated using multiple imputation for these participants, whose baseline characteristics did not generally vary from participants with observed retention in care status (Table C.1).

A total of 57 participants were found to be deceased by the end of follow-up activities, of which 24 and 39 deaths respectively had occurred by 24 and 36 months (Table 3.2); only 18 of these deaths had been recorded in original clinical records when follow-up study activities began, while the remainder were documented through study-initiated tracing procedures involving community health workers.

In total, retention in care status was confirmed through medical records or tracing activities for 744 (93%) participants at 24 months and 737 (92%) participants at 36 months; mortality status was confirmed 710 (89%) participants at 24 months and 700 (88%) at 36 months.

Table 3.2: Observed outcomes over time of participants in a 6-month trial of conditional economic incentives for clinic attendance provided at HIV treatment initiation, Tanzania, 2014-2018

	Total (n=800)	Control (n=112)	Intervention (n=688)
Retention in care*			
6 months	773/792 (97.6%)	102/111 (91.9%)	671/681 (98.5%)
12 months	724/783 (92.5%)	97/111 (87.4%)	627/672 (93.3%)
24 months	640/744 (86.0%)	94/111 (84.7%)	546/633 (86.3%)
36 months	607/737 (82.4%)	84/108 (77.8%)	523/629 (83.1%)
Mortality†			
6 months	6/789 (0.8%)	4/108 (3.7%)	2/681 (0.3%)
12 months	11/767 (1.4%)	6/108 (5.6%)	5/659 (0.8%)
24 months	24/710 (3.4%)	8/107 (7.5%)	16/603 (2.7%)
36 months	39/700 (5.6%)	9/104 (8.7%)	30/596 (5.0%)

Data are unadjusted observations. *The proportion with documented HIV clinic attendance within 90 days of the last scheduled appointment as of each timepoint. Participants missing outcomes are those who could not be traced and whose last known status indicated a transfer to another facility. †The proportion deceased at each timepoint. Participants missing outcomes are those who lacked confirmation of death or evidence of vitality.

Average treatment effects

In primary intention-to-treat analyses (Table 3.3), retention in care did not differ between the incentive and usual care groups at 24 months (86.5% v. 84.4%; RD=2.1, 95% CI: -5.2, 9.3) nor at 36 months (83.3% vs. 77.8%, RD=5.6, 95% CI: -2.7, 13.8). Likewise, there was no statistically significant difference in all-cause mortality at 24 months (2.5% vs. 7.7%, RD=-5.2, 95% CI: -10.5, 0.1) or at 36 months (4.7% vs. 9.0%, RD=-5.2, 95% CI: -10.2, 1.6).

Adjusted analyses yielded similar results, although with a slightly larger reduction in 24-month mortality among the incentive group that crossed the statistical significance threshold (RD=-5.7, 95% CI: -11.3, -0.1) while 36-month mortality differences remained non-significant. Estimates from complete-case analyses were also similar (Table C.2).

Table 3.3: Durability of effects from short-term conditional economic incentives for clinic attendance provided to HIV treatment initiates for 6 months, Tanzania, 2015-2018

		Group estimate (SE)				Between-group difference (95% CI)			
	N	Control		Intervention		Unadjusted		Adjusted*	
Retention in care†									
24 months	800	84.4%	(0.034)	86.5%	(0.013)	2.1	(-5.2, 9.3)	1.7	(-5.4, 8.9)
36 months	800	77.8%	(0.040)	83.3%	(0.015)	5.6	(-2.7, 13.8)	5.6	(-2.6, 13.9)
Mortality‡									
24 months	800	7.7%	(0.026)	2.5%	(0.006)	-5.2	(-10.5, 0.1)	-5.7	(-11.3, -0.1)
36 months	800	9.0%	(0.029)	4.7%	(0.008)	-4.3	(-10.2, 1.6)	-4.9	(-11.1, 1.2)

Data are estimates from logistic regression models adjusted for the health facility where randomization occurred. *Adjusted for baseline health facility, age, sex, and imbalanced baseline characteristics including language, occupation, and WHO Clinical Stage. †The proportion with documented HIV clinic attendance within 90 days of the last scheduled appointment as of each timepoint. Estimates were multiply imputed for 56 participants at 24 months and 63 participants at 36 months who could not be traced and whose last known status indicated a transfer to another facility. ‡The proportion deceased from any cause as of each timepoint. Estimates were multiply imputed for 90 participants at 24 months and 100 participants at 26 months who lacked confirmation of death or evidence of vitality (clinic visit on record or contact with tracing staff).

Effect heterogeneity

In sub-group analyses, estimated incentive effects on 24-month retention in care varied by age, wealth, and clinic, with larger (but not statistically significant) effects among younger individuals, those with low relative baseline wealth, and those enrolled at the regional hospital or health center compared to the large district hospital (Table C.3: p-interaction <0.20). There was no evidence of effect heterogeneity for 36-month retention or death at either timepoint.

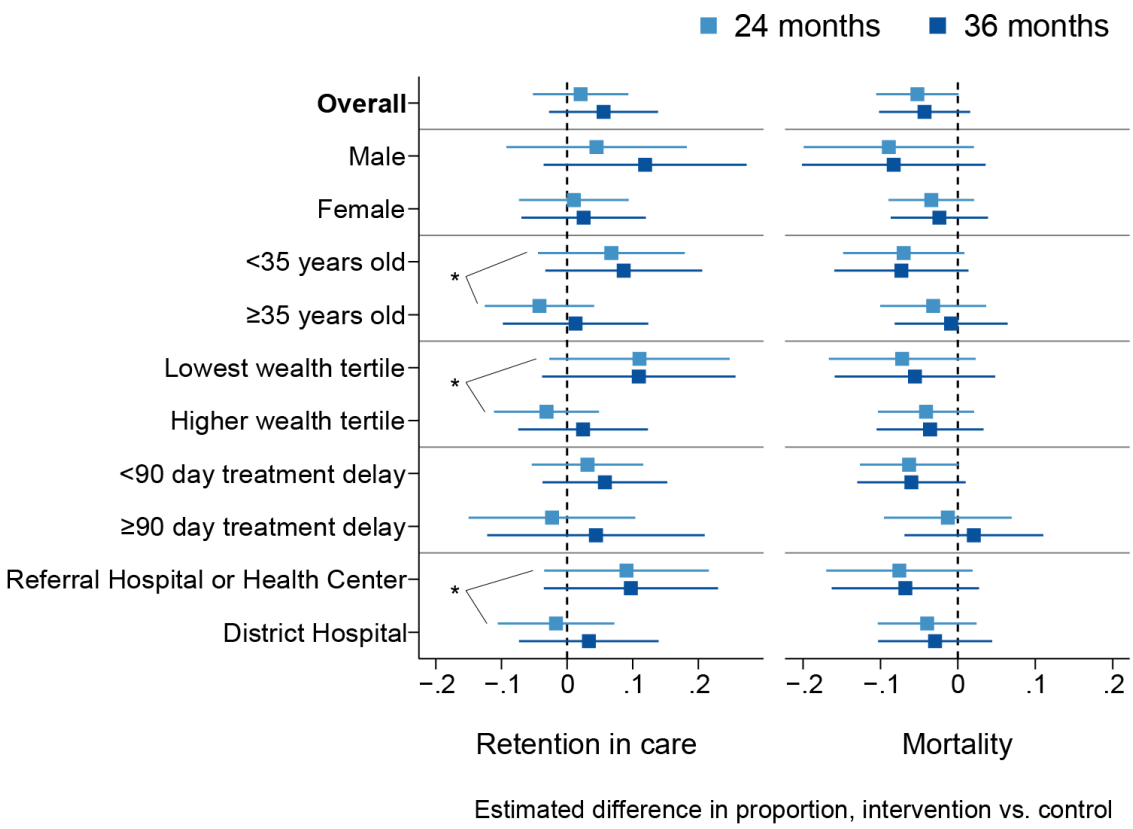

Figure 3.4: Heterogeneity in durability of effects from short-term conditional economic incentives provided to ART initiates by baseline characteristics, Tanzania, 2015-2018

*p-interaction <0.20

Survival analysis

Lastly, analysis of time to all-cause mortality did not reveal a significant difference in survival over 36 months (Figure 3.5). The incentive group had a significantly lower mortality rate during the first half of follow-up (p-interaction=0.076), including 12 months after the 6-month incentive period [0 to 18 months: hazard ratio (HR)=0.27, 95% CI: 0.10, 0.74]; thereafter, mortality rates did not significantly vary by intervention group (18 to 36 months: HR=1.13, 95% CI: 0.33, 3.79).

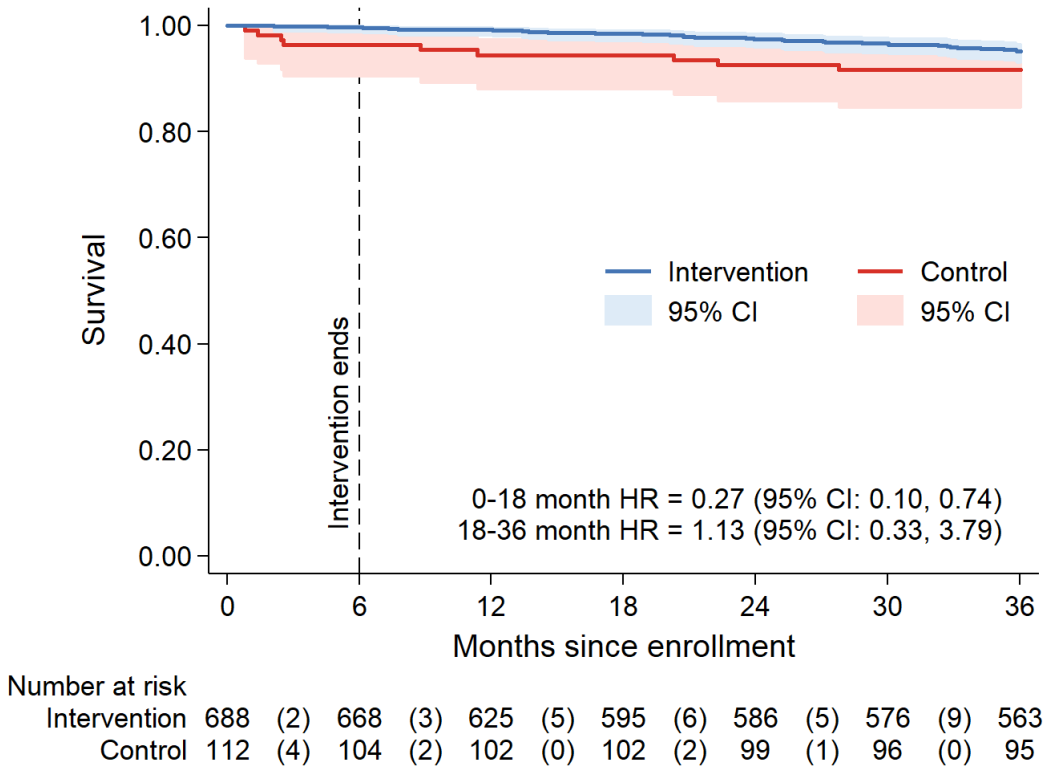

Figure 3.5: Kaplan-Meier survival plot of time to all-cause mortality among adult ART initiates in Tanzania, 2013-2018

3.4 Discussion

Gold-standard tracing procedures were used in a rare long-term follow-up study of short-term conditional economic incentives for treatment adherence to understand the durability of effects and assess any long-term harms or benefits. The results show that immediate improvements in retention and mortality from a 6-month incentive program for HIV treatment initiates[28] gradually declined over time, but did not drop below the comparison group as could occur if external rewards were to "crowd out" internal motivation. These findings help to address a dearth of information across the global medication adherence literature regarding enduring impacts of conditional economic incentives. To our knowledge, this is the first study to assess post-intervention effects beyond a year after the withdrawal of incentives for HIV treatment adherence.

After following up the original participants, this study did not find strong evidence that time-limited incentives produced lasting improvements in ART adherence. However, nor did

it find evidence for long-term harm. On the contrary, the results suggest that adherence gains during the incentive period may have averted early deaths at the start of HIV treatment, with lower mortality still perceptible at 18 months (and at 24 months in adjusted analyses). One possible explanation of these findings comes from a livelihood framework, whereby cash and food incentives are a "provision-type" intervention that is recommended to address basic needs of those most vulnerable; other interventions aimed at protecting and promoting livelihoods are recommended after providing this temporary stabilizing support.[34]] Another plausible mechanism for these findings is through the price pathway, whereby incentives lowered the cost associated with clinic attendance (including direct and opportunity costs) and triggered the initial adherence effect, then once the incentive was removed the behavior gradually reverted towards that of the control group as any habit formation effects gradually wore off. In the context of HIV, these findings indicate that short-term incentives are a simple, effective, and low-cost intervention for bolstering adherence through the difficult first months of ART initiation, a time commonly defined by stigma, illness, and loss of economic productivity[35] as well as peak loss to follow-up from clinical care.[76] However, additional "cash plus"[108] interventions may be necessary after ART initiation to address ongoing social and structural barriers to lifelong ART adherence, such as food insecurity and lack of funds for clinic transportation, along with behavioral challenges such as treatment fatigue;[109] linking complementary interventions to clinic attendance may also be important if the price pathway is key.

The original trial drew from principles of traditional and behavioral economics to focus on individuals starting HIV treatment, unlike other trials that have evaluated incentives for individuals already in care. The rationale for this design was the hypothesis that short-term incentives could provide essential support at the vulnerable time of ART initiation, while also promoting early habit formation to sustain ART adherence. Insights from psychology suggest that behavior changes during critical and sensitive periods may have lasting effects. Additionally, studies of other health-related behaviors demonstrated the potential for durable impacts even after the withdrawal of incentives. For example, one study found that cash incentives for gym attendance resulted in continued attendance even after payments were discontinued.[44] Another study indicated that short-term subsidies for antimalarial bednets produced a greater willingness to pay for bednets in the future.[45] This prior research supported the notion that short-term incentives could bolster individuals' motivation to continue various healthy behaviors after incentive periods have ended.

Alternatively, some scholars have theorized the possibility of eventual harm from short-term incentives. The "crowding-out" hypothesis suggests that the extrinsic motivation provided by incentives could have detrimental effects on free-choice intrinsic motivation, resulting in less inclination to continue the desired behavior after incentives end.[41] However, few studies of incentives for medication adherence have measured outcomes beyond the intervention period, leaving uncertainty around the ultimate impacts of short-term incentives.

The trial in this study initially followed participants for 12 months, 6 months after the end of the incentive period, and found continued although somewhat diminished effects on treatment adherence.[28] The original study also measured participants' intrinsic motivation for adherence at baseline, 6 months, and 12 months, finding that intrinsic motivation actually increased during and after the incentive period.[46] These findings motivated the current study's focus on long-term effects, alongside another study that measured the short-term durability of incentives' effects on ART adherence and found continued improvements in viral suppression and continuity of care in the United States 9 months after incentives ended.[110] These promising interim effects after the withdrawal of incentives set up the plausibility for longer-term impacts on HIV treatment adherence. Now, taken together with the results from this long-term study, the evidence suggests that effects of short-term incentives on ART adherence gradually decay over time but do not cause eventual harm.

This study had a number of limitations. First, the original trial was powered to detect effects at 6 and 12 months, not smaller effects as could be expected at longer follow-up intervals. Next, although exhaustive efforts were made to trace every original study participant, some individuals could not be located due to challenges including high mobility and frequently changed phone numbers. Additionally, potentially incomplete HIV care attendance records obtained at follow-up may have resulted in an underestimation of retention in care at intermediate time points, although any such misclassification is not anticipated to vary by study group. Lastly, participants in the original trial were recruited during a period when ART availability was limited to individuals with advanced disease progression, before recent policy changes extended universal access to ART immediately after HIV diagnosis; further long-term research on incentives for individuals starting ART in the 'Treat-All' era may be warranted. This study also had key strengths, including the original randomized design and focus on ART initiates, along with a rigorous tracing strategy to reduce outcome misclassification for participants no longer attending the original participating health facilities.

In conclusion, findings from this study suggest that small incentives are a safe and effective strategy to promote adherence at the critical time of HIV treatment initiation. Complementary strategies focused on sustaining lifelong treatment adherence are recommended after ART initiation to encompass a comprehensive approach to ending the HIV epidemic.

Conclusion

Addressing the social determinants of health is imperative to ending the HIV/AIDS epidemic. To reach the UNAIDS 95-95-95 goals for testing, uptake, and adherence to antiretroviral therapy (ART), health systems must provide patient-centered care that recognizes and accounts for socioeconomic barriers such as food insecurity, transportation costs, stigma, discrimination, and myriad other daily challenges facing people living with HIV. Conditional economic incentives, including cash and food assistance provided at clinic visits, are one promising strategy for supporting adherence in resource constrained settings and have been recommended within UNAIDS guidance on social protection. However, while the success of large-scale conditional cash transfer programs for poverty alleviation has led to proliferation of these programs around the world, a number of obstacles remain to widespread adoption of conditional economic incentives within HIV care. Prior literature contained gaps regarding the effectiveness of incentives for ART adherence, including impacts on a on biologic measure as well as underlying social determinants. Skeptics of incentives have also voiced concerns about sustainability and scalability, especially around the logistic and administrative burden of distributing incentives in clinical settings. Providers have also initially expressed hesitancy about paying patients to adhere to treatment that is already free and beneficial to them. Responding to these uncertainties, this work sought to strengthen the evidence base around the effectiveness and implementation of conditional economic incentives. In two randomized trials of adults initiating ART in Tanzania, incentives improved viral suppression, mitigated short-term food insecurity, and did not have harmful long-term effects. This work also demonstrated the potential feasibility to scale up incentives using mobile health technology (mHealth).

Chapter 1 explored the pathways through which incentives operate to improve adherence. This analysis evaluated whether cash and food incentives that were previously shown to improve retention and medication possession also mitigated established impediments. The results showed that food security, nutrition, and engagement in livelihood-generating activities improved across all study groups at 6 and 12 months after starting ART, underscoring the beneficial impacts of treatment on individual health and the ability to work. Incentives further reduced severe food insecurity relative to usual care during the first 6 months of treatment—while incentives were in place—but not nutrition or work status and did not have added effects at 12 months (when adherence gains were sustained). These results indicate

that modest cash and food assistance may help to alleviate the most severe food insecurity, and thereby facilitate adherence, at a critical time of heightened vulnerability and peak loss to follow-up shortly after starting treatment. However, small incentives such as those provided in this study likely do not constitute a large enough income effect to impact more moderate food insecurity, nutrition, or work status above and beyond the benefits of ART, and may primarily operate through the price effect by lowering costs associated with clinic attendance.

Chapter 2 was the first study to evaluate effects of clinic-based incentives on a biomarker of ART adherence among a general population in a resource constrained setting. This study also explored factors for optimal implementation, including the role of incentive size and the feasibility of delivery using mHealth. Participant attendance was monitored using biometrics and linked to electronic payments at monthly clinic visits for 6 months. Increasing incentive value was associated with more viral suppression at 6 months, while both amounts tested were more effective than the standard of care. The majority of payments were successfully distributed through mobile banking, which most participants had access and consented to, while a minority were given as cash in hand. These findings greatly strengthened the evidence base for the effectiveness of incentives at the time of treatment initiation, and contributed to our understanding of scalable implementation strategies.

Chapter 3 contributed to a dearth of evidence about the long-term effects of time-limited incentives. This analysis addressed the theoretical concern about incentives "crowding out" intrinsic motivation, versus alternate hypotheses of sustained benefits from habit formation or gradual attenuation of effects to zero. The results showed no difference in effects on retention in care or mortality at two to three years after enrollment in a 6-month incentive program. These findings do not provide evidence for either the crowding out or sustained benefit hypotheses, suggesting instead that benefits of incentives fade over time.

In conclusion, this work substantially adds to our understanding of the effectiveness and implementation of conditional economic incentives to improve antiretroviral therapy adherence. The food security analysis, one of few conducted in a randomized trial of incentives, brought additional attention to the importance of addressing severe food insecurity among individuals starting ART. Next, the viral suppression results provided critical biological evidence for the first time that incentives can clearly improve ART adherence. The comparisons of incentive size and the development of mobile technology for implementing incentives helped to pave the way for future successful scale-up. Lastly, the durability analysis served to alleviate concerns about potential long-term harm from incentives. Together, these findings demonstrate that small incentives are a safe and effective strategy to promote adherence at the time of ART initiation. Governments should give serious consideration to adopting economic incentives within HIV care programs in order to achieve the UNAIDS 95-95-95 goals.

Future research should further examine implementation of incentives at a larger scale and also investigate how and when to optimally pair incentives with other complementary strategies in order to sustain lifelong adherence. A planned cluster randomized controlled trial of the incentive program evaluated in Chapter 2, which will be conducted at 32 facilities in four regions of Tanzania, will shed light on factors including effectiveness, feasibility, and acceptability of incentives when implemented within health facilities under real-world conditions.[111] A pilot evaluation added on to this study will also examine an example of novel "cash plus" programming, whereby incentives are combined with other forms of support,[108] in this case targeted referral to community health workers for patients who may most benefit from more intensive intervention. This work will continue to add to the evidence base for patient-centered strategies to address social determinants of health, achieve HIV treatment and prevention targets, and end the HIV/AIDS epidemic.

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Appendix A

Appendix to Chapter 1

Table A.1: Predictors of censoring on all outcomes at both 6 and 12 months, food-insecure ART initiates in Tanzania, 2014-2016

	Overall			
	Missing* (n=104)	Observed (n=673)	Difference in means	*p value*†
Baseline Characteristics, mean				
Age (years)	35.3	37.2	-1.9	0.08
Female (%)	62.5	62.6	-0.1	0.99
Primary language is Swahili (%)	63.5	61.1	2.4	0.64
Christian religion (%)	69.2	75.6	-6.4	0.16
Primary education or higher (%)	61.5	60.5	1.1	0.84
Farmer (%)	44.2	52.6	-8.4	0.11
Married/partnership (%)	40.4	45.8	-5.4	0.31
Head of household (%)	57.7	63.0	-5.3	0.30
Household decision-making power (0-6)	4.65	4.97	-0.3	0.10
Household size (members)	3.41	3.76	-0.35	0.11
Nomadic housing tenure (%)	20.2	8.6	11.6	<0.001
Travel time to clinic (minutes)	43.7	47.1	-3.4	0.42
Travel cost to clinic (TZS)	1663	1434	228	0.34
Number of barriers to care (0-10)	2.28	2.10	0.18	0.30
Disclosed HIV status to ≥1 household member (%)	75.0	72.7	2.3	0.62
Household asset index (1-4)	2.34	2.52	-0.18	0.12
Owns a mobile phone (%)	52.9	63.3	-10.4	0.04
Days since ART started	25.1	28.3	-3.2	0.23
CD4 cell count (cells/μL)	182.9	206.5	-23.6	0.17
WHO clinical stage 3-4 (%)	62.5	57.5	5.0	0.34
Self-rated health (1-10)	7.82	8.21	-0.39	0.01
Expect better health in 1 year (%)	31.7	44.6	-12.8	0.01
Baseline Outcome Values, mean				
HHS severe (%)	40.4	41.8	-1.4	0.79
HFIAS (0-27)	16.4	15.9	0.5	0.37
IDDS (0-9)	5.26	5.28	-0.02	0.78
Weight (kg)	55.2	56.5	-1.3	0.19
BMI (kg/m^2)	21.0	21.5	-0.5	0.17
Currently working (%)	48.1	60.0	-12.0	0.02
Functional limitation (%)	57.7	55.6	2.1	0.69
0–6 Month Adherence, mean				
MPR≥95% (%)	59.6	82.5	-22.9	<0.001

TZS, Tanzanian Shillings; WHO, World Health Organization; HHS, Household Hunger Scale; HFIAS, Household Food Insecurity Access Scale; IDDS, Individual Dietary Diversity Scale; BMI, body-mass index; MPR, Medication Possession Ratio. *For the purposes of this table, missing is defined as missing all outcomes at both 6 and 12 months, i.e. complete loss to study follow-up. (This definition was not used in primary analyses, which used inverse probability of censoring weights based on missing the outcome of interest for each model.) †T-test for difference in means.

Table A.2: Characteristics of women pregnant at baseline

	Pregnant (n=23)	
Age (years)	26.3	(4.6)
Primary language is Swahili	12	(52.2%)
No formal education	5	(21.7%)
Farmer	5	(21.7%)
Married/partnership	18	(78.3%)
Head of household	5	(21.7%)
Household size (members)	3.0	(1.22)
Travel time to clinic (minutes)	40.9	(26.0)
Travel cost to clinic (TZS)	1091	(1526)
Asset index (1-4)	2.9	(1.1)
Time since ART started (days)	40.1	(26.2)
CD4 cell count (cells/μL)	501.9	(217.9)
WHO clinical stage 3-4	2	(8.7%)
Food Security		
HHS severe	5	(21.7%)
HFIAS (0-27)	14.0	(5.8)
IDDS (0-9)	5.0	(0.8)
Nutritional Status		
BMI (kg/m^2)	24.2	(3.4)
Weight (kg)	62.0	(9.9)
Livelihood		
Currently working	8	(34.8%)
Functional limitation	5	(21.7%)

Data are n (%) or mean (SD).

Table A.3: Sensitivity analysis including pregnant women: adjusted inverse probability of censoring weighted effects of cash or food transfers for HIV-infected adults, Tanzania, 2014-2016.

		Difference-in-Differences Average Treatment Effect* (95% CI)					
	N†	Cash vs. Comparison		Food vs. Comparison		Cash vs. Food	
6 Months							
Food Security							
HHS severe (%)	438	-22.6	(-42.5, -2.7)	-22.8	(-42.3, -3.2)	0.2	(-12.6, 12.9)
HFIAS (0-27)	437	-1.70	(-4.89, 1.48)	-1.52	(-4.67, 1.62)	-0.18	(-2.10, 1.74)
IDDS (0-9)	466	-0.03	(-0.47, 0.40)	-0.01	(-0.45, 0.42)	-0.02	(-0.25, 0.21)
Nutritional Status							
BMI (kg/m^2)	656	-0.01	(-0.48, 0.46)	0.12	(-0.37, 0.61)	-0.13	(-0.51, 0.25)
Weight (kg)	675	-0.01	(-1.24, 1.22)	0.31	(-0.97, 1.58)	-0.32	(-1.26, 0.63)
Livelihood							
Currently working (%)	465	-5.1	(-25.2, 15.0)	-1.3	(-21.7, 19.0)	-3.8	(-17.7, 10.1)
12 Months							
Food Security							
HHS severe (%)	462	3.3	(-15.2, 21.7)	-0.1	(-18.3, 18.1)	3.4	(-10.0, 16.7)
HFIAS (0-27)	462	0.48	(-2.28, 3.23)	1.14	(-1.54, 3.82)	-0.66	(-2.50, 1.18)
IDDS (0-9)	462	-0.09	(-0.40, 0.22)	0.14	(-0.19, 0.46)	-0.22	(-0.49, 0.04)
Nutritional Status							
BMI (kg/m^2)	568	0.25	(-0.41, 0.91)	0.08	(-0.55, 0.71)	0.18	(-0.39, 0.74)
Weight (kg)	582	0.68	(-1.01, 2.36)	0.38	(-1.26, 2.02)	0.30	(-1.09, 1.69)
Livelihood							
Currently working (%)	457	-6.4	(-26.1, 13.2)	0.9	(-18.4, 20.0)	-7.4	(-21.1, 6.3)
Functional limitation (%)	350	-12.2	(-42.8, 18.4)	-9.8	(-40.2, 20.6)	-2.4	(-18.9, 14.0)

Data are modified intention-to-treat estimates (excluding 5 participants who did not receive allocated intervention) from generalized estimating equation (GEE) models: with Gaussian distribution and identity link; adjusted for clinic, baseline imbalances [age, occupation, WHO stage, and weight (except for weight and BMI models)], and prognostic factors (sex, education, head of household, household size, asset index, and lean season); and weighted with inverse probability of censoring weights estimated by treatment group, baseline characteristics, baseline values for HHS severe, HFIAS, IDDS, weight, currently working, and functional limitation, and 0-6 month or 0-12 month MPR$\geq$95%. Separate models were estimated for the change from baseline to 6 months and the change from baseline to 12 months due to non-monotone missingness, whereby some participants were observed at 12 months but not 6 months and vice versa. HHS, Household Hunger Scale; HFIAS, Household Food Insecurity Access Scale; IDDS, Individual Dietary Diversity Scale; BMI, body-mass index. *Between-group difference in the change from baseline in percentage point or continuous value at 6 and 12 months. †Number of subjects with fully observed baseline covariates (missing n=7) and the outcome observed at the specified follow-up time (6 or 12 months) out of 800 total subjects.

Table A.4: Sensitivity analysis: unadjusted inverse probability of censoring weighted effects of cash or food transfers on food security, nutritional status, and livelihoods, Tanzania, 2014-2016.

	N†	Difference-in-Differences Average Treatment Effect* (95% CI)					
		Cash vs. Comparison		Food vs. Comparison		Cash vs. Food	
6 Months							
Food Security							
HHS severe (%)	430	-21.9	(-42.0, -1.7)	-20.3	(-40.5, -0.05)	-1.6	(-12.7, 9.5)
HFIAS (0-27)	429	-1.35	(-4.35, 1.66)	-1.03	(-4.06, 2.00)	-0.31	(-1.97, 1.34)
IDDS (0-9)	458	0.03	(-0.33, 0.39)	0.06	(-0.30, 0.42)	-0.03	(-0.22, 0.17)
Nutritional Status							
BMI (kg/m^2)	640	0.02	(-0.38, 0.42)	0.20	(-0.21, 0.60)	-0.18	(-0.47, 0.12)
Weight (kg)	657	0.08	(-0.98, 1.13)	0.53	(-0.54, 1.60)	-0.45	(-1.19, 0.29)
Livelihood							
Currently working (%)	457	-6.7	(-24.0, 10.5)	-4.1	(-21.9, 13.6)	-2.6	(-14.3, 9.0)
12 Months							
Food Security							
HHS severe (%)	451	4.0	(-12.7, 20.7)	1.3	(-15.4, 18.1)	2.7	(-8.5, 13.9)
HFIAS (0-27)	451	0.54	(-1.80, 2.88)	1.23	(-1.10, 3.55)	-0.69	(-2.22, 0.85)
IDDS (0-9)	451	-0.11	(-0.38, 0.15)	0.11	(-0.17, 0.39)	-0.22	(-0.44, 0.00)
Nutritional Status							
BMI (kg/m^2)	554	0.27	(-0.27, 0.82)	0.15	(-0.36, 0.67)	0.12	(-0.34, 0.57)
Weight (kg)	567	0.72	(-0.68, 2.12)	0.60	(-0.75, 1.95)	0.12	(-1.00, 1.25)
Livelihood							
Currently working (%)	447	-7.1	(-23.9, 9.7)	0.2	(-16.4, 16.7)	-7.2	(-18.3, 3.9)
Functional limitation (%)	345	-11.3	(-36.8, 14.3)	-11.3	(-36.8, 14.2)	0.0	(-14.0, 14.0)

Data are modified intention-to-treat estimates (excluding 23 pregnant women and 5 participants who did not receive allocated intervention) from generalized estimating equation (GEE) models: with Gaussian distribution and identity link; and weighted with inverse probability of censoring weights estimated by treatment group, baseline characteristics, baseline values for HHS severe, HFIAS, IDDS, weight, currently working, and functional limitation, and 0-6 month or 0-12 month MPR$\geq$95%. Separate models were estimated for the change from baseline to 6 months and the change from baseline to 12 months due to non-monotone missingness, whereby some participants were observed at 12 months but not 6 months and vice versa. HHS, Household Hunger Scale; HFIAS, Household Food Insecurity Access Scale; IDDS, Individual Dietary Diversity Scale; BMI, body-mass index. *Between-group difference in the change from baseline in percentage point or continuous value at 6 and 12 months. †Number of subjects with fully observed baseline covariates included in weights (missing n=7) and the outcome observed at the specified follow-up time (6 or 12 months) out of 777 total included subjects.

Table A.5: Sensitivity analysis: Complete case unweighted adjusted effects of cash or food transfers on food security, nutritional status, and livelihoods, Tanzania, 2014-2016.

		Difference-in-Differences Average Treatment Effect* (95% CI)					
	N†	Cash vs. Comparison		Food vs. Comparison		Cash vs. Food	
6 Months							
Food Security							
HHS severe (%)	430	-2.2	(-24.4, 20.0)	-6.2	(-28.5, 16.0)	4.0	(-9.5,17.6)
HFIAS (0-27)	429	0.20	(-2.29, 2.69)	-0.72	(-3.22, 1.78)	0.93	(-0.84, 2.69)
IDDS (0-9)	458	-0.14	(-0.53, 0.25)	-0.15	(-0.54, 0.25)	0.00	(-0.23, 0.24)
Nutritional Status							
BMI (kg/m^2)	640	0.05	(-0.37, 0.48)	0.21	(-0.21, 0.63)	-0.16	(-0.50, 0.19)
Weight (kg)	657	0.19	(-0.93, 1.31)	0.57	(-0.55, 1.69)	-0.38	(-1.25, 0.49)
Livelihood							
Currently working (%)	457	6.5	(-12.3, 25.3)	5.4	(-13.9, 24.8)	1.0	(-13.2, 15.3)
12 Months							
Food Security							
HHS severe (%)	451	-4.2	(-25.0, 16.7)	-5.1	(-25.7, 15.6)	-0.9	(-13.0, 14.8)
HFIAS (0-27)	451	-0.08	(-2.98, 2.82)	-0.11	(-2.92, 2.71)	0.03	(-1.85, 1.91)
IDDS (0-9)	451	0.01	(-0.32, 0.34)	0.17	(-0.17, 0.51)	-0.16	(-0.43, 0.11)
Nutritional Status							
BMI (kg/m^2)	554	0.25	(-0.39, 0.90)	0.24	(-0.37, 0.85)	0.01	(-0.51, 0.54)
Weight (kg)	567	0.72	(-0.93, 2.37)	0.76	(-0.83, 2.36)	0.04	(-1.35, 1.26)
Livelihood							
Currently working (%)	447	-5.7	(-26.0, 14.6)	-0.2	(-19.9, 19.6)	-5.5	(-20.1, 9.1)
Functional limitation (%)	345	-10.9	(-39.0, 17.3)	-7.0	(-35.6, 21.5)	-3.8	(-21.5, 13.8)

Data are modified intention-to-treat estimates (excluding 23 pregnant women and 5 participants who did not receive allocated intervention) from generalized estimating equation (GEE) models: with Gaussian distribution and identity link; using Bonferroni's correction for multiple comparisons; and adjusted for clinic, baseline imbalances [age, occupation, WHO stage, and weight (except for weight and BMI models)], and prognostic factors (sex, education, head of household, household size, asset index, and lean season). Inverse probability of censoring weights (IPCW) used in the primary analysis were not applied for these models. *Between-group difference in the change from baseline in percentage point or continuous value at 6 and 12 months. †Number of subjects with fully observed baseline covariates (missing n=7) and the outcome observed at the specified follow-up time (6 or 12 months) out of 777 total included subjects.

Appendix B

Appendix to Chapter 2

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

		Group estimate (SE)*			Between-group difference (95% CI)*		
Outcome at 6 months	N	0 TZS	10000 TZS	22500 TZS	10000 vs. 0	22500 vs. 0	22500 vs. 10000
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)	13.3 (4.8, 21.7)	3.5 (-4.3, 11.2)
Retained in care	530	83.7% (0.027)	88.3% (0.024)	90.9% (0.022)	4.5 (-2.6, 11.6)	7.1 (0.4, 13.9)	2.6 (-3.8, 9.0)
Virally suppressed‡	464	86.8% (0.030)	93.8% (0.021)	95.0% (0.018)	6.9 (0.0, 13.9)	8.1 (1.2, 15.0)	1.2 (-4.3, 6.6)
Appointment attendance (%)§	530	80.0% (0.017)	87.4% (0.017)	90.6% (0.017)	7.4 (2.8, 12.1)	10.6 (5.9, 15.2)	3.1 (-1.6, 7.9)
Total number of visits attended	530	4.29 (0.127)	4.83 (0.131)	5.03 (0.130)	0.54 (0.18, 0.90)	0.73 (0.38, 0.11)	0.19 (-0.17, 0.56)

Data are estimates from generalized linear models adjusted for the clinic where randomization 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.

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

		Group estimate (SE)*			Between-group difference (95% CI)*		
Outcome at 6 months	N	0 TZS	10000 TZS	22500 TZS	10000 vs. 0	22500 vs. 0	22500 vs. 10000
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)	12.6 (4.2, 21.0)	3.4 (-4.3, 11.2)
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)	5.9 (-0.3, 12.0)	1.0 (-4.0, 6.0)

Data are estimates from logistic regression models adjusted for the clinic where randomization 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.

Table B.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

		Group estimate (SE)*				Between-group		
	N	Control		Intervention		difference (95% CI)*		*p-interaction*
Overall	530	73.0%	(0.034)	84.5%	(0.020)	11.5	(3.8, 19.1)	
Sex								
Male	200	68.2%	(0.061)	84.3%	(0.032)	16.1	(2.7, 29.5)	ref.
Female	330	75.9%	(0.041)	84.6%	(0.025)	8.7	(-0.6, 18.1)	0.45
Age								
18-24 years	66	67.6%	(0.097)	85.0%	(0.059)	17.4	(-4.9, 39.7)	ref.
25-34 years	203	65.9%	(0.059)	83.9%	(0.032)	18.0	(4.9, 31.2)	0.99
$\geq$35 years	261	80.0%	(0.044)	84.8%	(0.027)	4.9	(-5.4, 15.1)	0.38
Wealth index								
Low	177	68.2%	(0.063)	87.1%	(0.031)	18.9	(5.1, 32.7)	ref.
Middle	177	68.7%	(0.058)	82.6%	(0.037)	13.9	(0.4, 27.5)	0.50
High	176	83.1%	(0.053)	83.6%	(0.035)	0.5	(-11.9, 12.9)	0.068
Treatment delay								
0-1 days	169	64.2%	(0.066)	83.1%	(0.036)	18.9	(4.0, 33.8)	ref.
2-7 days	204	78.9%	(0.049)	88.7%	(0.030)	9.8	(-1.0, 20.7)	0.62
$>$1 week	157	74.0%	(0.062)	80.8%	(0.039)	6.8	(-7.4, 21.0)	0.26

Data are estimates from logistic regression models adjusted for the clinic where randomization 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.

Appendix C

Appendix to Chapter 3

Table C.1: Comparison of baseline characteristics between participants with observed versus missing outcomes at 36 months

	Retention in care		Mortality	
	Observed (n=737)	Missing (n=63)	Observed (n=700)	Missing (n=100)
Treatment arm				
Control	108 (96.4%)	4 (3.6%)	104 (92.9%)	8 (7.1%)
Intervention	629 (91.4%)	59 (8.6%)	596 (86.6%)	92 (14.4%)
Participant's sex				
Male	265 (91.1%)	26 (8.9%)	244 (83.8%)	47 (16.2%)
Female	472 (92.7%)	37 (7.3%)	456 (89.6%)	53 (10.4%)
Age				
<35 years old	347 (91.1%)	34 (8.9%)	328 (86.1%)	53 (13.9%)
≥35 years old	390 (93.1%)	29 (6.9%)	372 (88.8%)	47 (11.2%)
Marital status				
Married or partnered	327 (94.8%)	18 (5.2%)	314 (91.0%)	31 (9.0%)
Not married or separated	410 (90.1%)	45 (9.9%)	386 (84.8%)	69 (15.2%)
Language				
Swahili	452 (92.4%)	37 (7.6%)	426 (87.1%)	63 (12.9%)
Sukuma or other	285 (91.6%)	26 (8.4%)	274 (88.1%)	37 (11.9%)
Educational attainment				
Some pre-/primary school	112 (92.6%)	9 (7.4%)	105 (86.8%)	16 (13.2%)
Primary school	406 (92.9%)	31 (7.1%)	382 (87.4%)	55 (12.6%)
Secondary school or more	46 (95.8%)	2 (4.2%)	46 (95.8%)	2 (4.2%)
No formal education	173 (89.2%)	21 (10.8%)	167 (86.1%)	27 (13.9%)
Occupation				
Farmer	371 (91.6%)	34 (8.4%)	353 (87.2%)	52 (12.8%)
Business	102 (97.1%)	3 (2.9%)	97 (92.4%)	8 (7.6%)
Other	166 (91.7%)	15 (8.3%)	159 (87.8%)	22 (12.2%)
Unemployed	98 (89.9%)	11 (10.1%)	91 (83.5%)	18 (16.5%)
Currently working				
No	308 (91.1%)	30 (8.9%)	292 (86.4%)	46 (13.6%)
Yes	429 (92.9%)	33 (7.1%)	408 (88.3%)	54 (11.7%)
Wealth index				
Lowest wealth tertile	267 (92.4%)	22 (7.6%)	255 (88.2%)	34 (11.8%)
Higher wealth tertile	470 (92.0%)	41 (8.0%)	445 (87.1%)	66 (12.9%)
Facility				
Referral Hospital	179 (95.2%)	9 (4.8%)	177 (94.1%)	11 (5.9%)
District Hospital	474 (90.6%)	49 (9.4%)	438 (83.7%)	85 (16.3%)
Health Center	84 (94.4%)	5 (5.6%)	85 (95.5%)	4 (4.5%)
WHO clinical stage				
Stage 1	108 (95.6%)	5 (4.4%)	104 (92.0%)	9 (8.0%)
Stage 2	214 (92.2%)	18 (7.8%)	203 (87.5%)	29 (12.5%)
Stage 3	375 (91.2%)	36 (8.8%)	358 (87.1%)	53 (12.9%)
Stage 4	40 (90.9%)	4 (9.1%)	35 (79.5%)	9 (20.5%)
Time on ART (days)	14.0 (12-44)	14.0 (14-42)	14.0 (12-44)	23.5 (14-45)
Treatment delay				
<90 days	573 (91.2%)	55 (8.8%)	536 (85.4%)	92 (14.6%)
≥90 days	164 (95.3%)	8 (4.7%)	164 (95.3%)	8 (4.7%)

Data are n (%) or median (IQR). ART=antiretroviral therapy. WHO=World Health Organization.

Table C.2: Complete case sensitivity analysis of the durability of effects from short-term conditional economic incentives provided to HIV treatment initiates for 6 months, Tanzania, 2015-2018

		Group estimate (SE)				Between-group difference (95% CI)			
	N	Control		Intervention		Unadjusted		Adjusted*	
Retention in care†									
24 months	744	84.7%	(0.034)	86.3%	(0.014)	1.5	(-5.6, 8.7)	1.1	(-5.9, 8.1)
36 months	737	77.8%	(0.040)	83.2%	(0.015)	5.4	(-2.9, 13.7)	5.2	(-3.0, 13.4)
Mortality‡									
24 months	710	7.5%	(0.025)	2.7%	(0.007)	-4.8	(-9.9, 0.3)	-5.2	(-10.6, 0.1)
36 months	700	8.5%	(0.027)	5.0%	(0.009)	-3.5	(-9.0, 2.1)	-3.9	(-9.7, 1.9)

Data are estimates from logistic regression models adjusted for health facility where randomization occurred. *Adjusted for baseline health facility, age, sex, and imbalanced baseline characteristics including language, occupation, and WHO Clinical Stage. †The proportion with evidence of HIV clinic attendance at the time of interest. Excludes those among the original 800 participants who were not successfully traced if the last known status indicated a transfer to another facility. ‡The proportion deceased among those with confirmation of death or evidence of vitality (clinic visit on record or contact with tracing staff) as of the time of interest.

Table C.3: Heterogeneity in durability of effects from short-term (6-month) conditional economic incentives provided to HIV treatment initiates by baseline characteristics, Tanzania, 2015-2018.

		Group estimate (SE)				Between-group		*p-int*
	N	Control		Intervention		difference (95% CI)		
Retention in care at 24 months	800	84.4%	(0.034)	86.5%	(0.013)	2.1	(-5.2, 9.3)	
Male	291	78.9%	(0.066)	83.4%	(0.024)	4.5	(-9.2, 18.2)	0.73
Female	509	87.3%	(0.039)	88.3%	(0.016)	1.0	(-7.3, 9.4)	
<35 years old	381	78.3%	(0.053)	85.1%	(0.021)	6.7	(-4.4, 17.9)	0.16
≥35 years old	419	91.9%	(0.021)	87.7%	(0.018)	-4.2	(-12.5, 4.1)	
Below median wealth	400	75.7%	(0.067)	86.7%	(0.022)	11.0	(-2.7, 24.8)	0.08
Above median wealth	400	89.5%	(0.037)	86.4%	(0.017)	-3.1	(-11.1, 4.9)	
≤90 day treatment delay	628	82.7%	(0.040)	85.8%	(0.015)	3.1	(-5.4, 11.6)	0.56
>90 day treatment delay	172	91.2%	(0.059)	88.9%	(0.026)	-2.3	(-15.0, 10.4)	
Referral hospital/health center	277	82.1%	(0.061)	91.2%	(0.019)	9.0	(-3.5, 21.6)	0.12
District hospital	523	85.7%	(0.042)	84.0%	(0.018)	-1.7	(-10.6, 7.2)	
Retention in care at 36 months	800	77.8%	(0.040)	83.3%	(0.015)	5.6	(-2.7, 13.8)	
Male	291	68.3%	(0.074)	80.2%	(0.026)	11.9	(-3.6, 27.3)	0.38
Female	509	82.6%	(0.045)	85.2%	(0.017)	2.5	(-6.9, 12.0)	
<35 years old	381	73.1%	(0.057)	81.8%	(0.023)	8.6	(-3.3, 20.6)	0.44
≥35 years old	419	83.4%	(0.023)	84.7%	(0.020)	1.3	(-9.8, 12.4)	
Below median wealth	400	72.2%	(0.071)	83.1%	(0.025)	10.9	(-3.8, 25.6)	0.36
Above median wealth	400	81.0%	(0.047)	83.5%	(0.018)	2.4	(-7.4, 12.3)	
≤90 day treatment delay	628	76.6%	(0.046)	82.4%	(0.017)	5.8	(-3.7, 15.3)	0.98
>90 day treatment delay	172	82.3%	(0.080)	86.7%	(0.028)	4.4	(-12.2, 21.0)	
Referral hospital/health center	277	79.6%	(0.064)	89.3%	(0.021)	9.7	(-3.5, 23.0)	0.30
District hospital	523	76.8%	(0.051)	80.2%	(0.020)	3.3	(-7.3, 13.9)	
Mortality at 24 months	800	7.7%	(0.026)	2.5%	(0.006)	-5.2	(-10.5, 0.1)	
Male	291	12.0%	(0.055)	3.1%	(0.011)	-8.9	(-19.9, 2.1)	0.60
Female	509	5.6%	(0.027)	2.1%	(0.007)	-3.4	(-9.0, 2.1)	
<35 years old	381	9.1%	(0.039)	2.1%	(0.008)	-7.0	(-14.8, 0.8)	0.40
≥35 years old	419	6.1%	(0.008)	2.9%	(0.009)	-3.2	(-10.0, 3.6)	
Below median wealth	400	8.8%	(0.048)	1.6%	(0.008)	-7.2	(-16.7, 2.3)	0.38
Above median wealth	400	7.1%	(0.031)	3.0%	(0.008)	-4.1	(-10.3, 2.1)	
≤90 day treatment delay	628	8.7%	(0.032)	2.4%	(0.007)	-6.3	(-12.6, 0.0)	0.45
>90 day treatment delay	172	4.1%	(0.040)	2.8%	(0.014)	-1.3	(-9.6, 7.0)	
Referral hospital/health center	277	10.1%	(0.047)	2.5%	(0.010)	-7.6	(-17.0, 1.9)	0.59
District hospital	523	6.4%	(0.031)	2.5%	(0.008)	-4.0	(-10.3, 2.4)	
Mortality at 36 months	800	9.0%	(0.029)	4.7%	(0.008)	-4.3	(-10.2, 1.6)	
Male	291	13.2%	(0.059)	4.9%	(0.014)	-8.3	(-20.2, 3.6)	0.42
Female	509	7.0%	(0.030)	4.6%	(0.010)	-2.4	(-8.7, 3.9)	
<35 years old	381	11.2%	(0.043)	3.9%	(0.011)	-7.3	(-16.0, 1.4)	0.24
≥35 years old	419	6.3%	(0.011)	5.4%	(0.012)	-0.9	(-8.2, 6.4)	
Below median wealth	400	9.7%	(0.051)	4.2%	(0.013)	-5.6	(-15.9, 4.8)	0.71
Above median wealth	400	8.6%	(0.033)	5.0%	(0.011)	-3.6	(-10.5, 3.3)	
≤90 day treatment delay	628	10.3%	(0.035)	4.3%	(0.009)	-6.0	(-13.0, 1.0)	0.24
>90 day treatment delay	172	4.2%	(0.041)	6.3%	(0.020)	2.1	(-6.9, 11.0)	
Referral hospital/health center	277	10.2%	(0.047)	3.4%	(0.012)	-6.8	(-16.3, 2.7)	0.36
District hospital	523	8.4%	(0.036)	5.4%	(0.011)	-2.9	(-10.3, 4.4)	