REDUCING POST-HOSPITAL MORTALITY IN HIV-INFECTED ADULTS IN TANZANIA (DARAJA)

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Protocol Summary

Title: Reducing Post-hospital Mortality in HIV-infected Adults in Tanzania (DARAJA)

Population: Five-hundred hospitalized HIV-infected adults who are being discharged home and transitioning from the hospital to outpatient HIV care clinic.

Entry criteria include:

- Antiretroviral naïve or defaulted for > 7 days.
- Lives inMwanza region (defined)
- Will be referred to clinic in Mwanza region
- Has mobile phone or access to mobile phone
- Planning to stay in Mwanza region for the next 24 months
- Able to speak Kiswahili or English
- Capable and willing to provide informed consent
- Willing to provide locator information and 2 designated contact persons
- Willing to have a home visit from a study team member

Site: Mwanza, Tanzania

Study Duration: 48 months

Subject Duration: 24 months

Objectives: To evaluate the efficacy of the DARAJA social worker intervention versus standard of care to increase the 1-year survival rate in 500 HIV-infected adults consecutively discharged from hospitals in Mwanza region including Bugando Medical Center, Sekou Toure Regional Referral Hospital, Buzuruga Health Center, Nyamagana District Hospital, and hospitals in Misungwi, Sengerema, and Magu districts.

Primary hypotheses: One-year survival will be 90% in the intervention group versus 75% in the control group.

Primary study endpoint and analysis: The primary endpoint is survival at one year. We will have >80% power to detect the 15% absolute difference in survival at $p<0.05$.

Secondary endpoints and analysis: 1. HIV care continuum: Evaluate the effect of the intervention on linkage to care and other steps in the care continuum including retention, adherence, and achieving virologic suppression at 1 year. 2. Gelberg and Andersen Model: Use structural equation modelling to analyze the effect of the intervention on factors in the model and their effect upon linkage and survival. 3. Acceptability: Conduct in-depth interviews with a subset of study participants and health care workers to evaluate acceptability of DARAJA and factors associated with linkage to care. 4. Cost: Evaluate the incremental cost of the intervention and cost per life saved.

SPECIFIC AIMS: Hospitalization of HIV-infected adults in Africa is often the last opportunity to initiate and maintain life-saving HIV care. Our data in Tanzania (1) and studies from other African countries (2–10) show that ≥ 20% of adult admissions to medical wards in Africa are related to HIV. Furthermore, only 60% of the HIV-infected adults who are discharged after a hospitalization survive for one year (11–14). This high mortality persists despite implementation of World Health Organization (WHO) guidelines which recommend "rapid initiation" of ART within 7 days (15). In the only published report of initiating rapid ART for hospitalized patients in Africa, the 6-month survival was still only **75%** (16). Our own data and other data suggest that this **post-hospital mortality** is strongly associated with **failure to link to the HIV clinic** after discharge (11,13,14).

HIV-infected hospitalized patients are easily identified, temporarily "captive", and at high risk for death. They need a **differentiated model of care** to introduce and keep them in the HIV care continuum and to improve their survival. The transition from the hospital to an outpatient HIV clinic is currently a major lesion. There have been **no randomized trials** in Africa studying the optimal strategy to transition HIV-infected adults from the hospital to the clinic. We conducted formative research in Mwanza, Tanzania to understand why HIV-infected adults discharged from the hospital fail to link to HIV primary care. This research utilized the **Gelberg and Andersen Behavioral Model of Health Services Utilization for Vulnerable Populations** (17–19). Eight factors were associated with poor linkage including: unemployment, traditional health beliefs, low self-efficacy, lack of transportation, lack of social support, stigma, low perceived need for HIV care, and physical weakness.

To address these factors, we **adapted** and **pilot-tested** an evidenced-based **social worker intervention** (ARTAS), which has been effective in linking HIV-infected patients to primary care in the United States (20,21). A social worker meets each patient **five times** to facilitate linkage to outpatient HIV care. The first meeting occurs in the hospital, the second at the patient's home, and meetings 3-5 occur in the home or in the HIV clinic. The social worker reviews the eight factors in the Gelberg and Andersen Model, inquires about other barriers to linkage, and then helps patients to use their own strengths, abilities, and resources to address these barriers. We call our intervention **DARAJA** (Kiswahili for **BRIDGE**) since the social worker acts as a bridge helping the patient transition from the hospital to the clinic. We piloted this intervention in 31 HIV-infected adults hospitalized in Mwanza, Tanzania. All 31 (**100%**) participants were **linked** to the HIV clinic within 1 month compared to **63%** of historical controls. Twenty-eight (**90%**) were **alive at one year** compared to **75%** of historical controls.

Based on these pilot data, we propose a **randomized clinical trial** at hospitals in Mwanza region, including Bugando Medical Center, Sekou Toure Regional Referral Hospital, Buzuruga Health Center, and Nyamagana District Hospital, and hospitals in Misungwi, Sengerema and Magu districts, and their associate HIV clinics. We hypothesize the DARAJA social worker intervention will increase post-hospital survival from 75% to 90%.

Primary Aim: To evaluate the efficacy of the DARAJA social worker intervention versus standard of care to increase the 1-year **survival** rate in **500** HIV-infected adults consecutively discharged from study hospitals in Mwanza. We hypothesize that the one-year survival will be **90%** in the intervention group **vs. 75%** in the control group. We will have >80% power to detect this 15% absolute difference in survival at $p<0.05$.

Secondary Aims:

1. **HIV care continuum:** Evaluate the effect of the intervention on linkage to care and other steps in the care continuum including retention, adherence, and achieving virologic suppression at 1 year.
2. **Gelberg and Andersen Model:** Use structural equation modelling to analyze the effect of the intervention on factors in the model and their effect upon linkage and survival.
3. **Acceptability:** Conduct in-depth interviews with a subset of study participants and health care workers to evaluate acceptability of DARAJA and factors associated with linkage to care.
4. **Cost:** Evaluate the incremental cost of the intervention and cost per life saved

The goal of this proposal is to develop a model of care for hospitalized HIV-infected adults to improve their linkage to the outpatient HIV clinic and their post-hospital **survival** in response to **NIH PA-17-182**. Improving post-hospital outcomes for HIV-infected adults could save **several hundred thousand** lives across Africa each year. After the successful completion of this trial, we will conduct implementation studies with our partners in the Tanzanian Ministry of Health to demonstrate scalability and cost-effectiveness.

RESEARCH STRATEGY

A. SIGNIFICANCE. Interventions to reduce HIV-related mortality are urgently needed. Over one million people died from AIDS in 2016, and more than 90% of these HIV-related deaths occurred in Africa (22). Several recent trials of new interventions for HIV-infected outpatients have demonstrated improved survival. Rapid ART initiation on the same day as HIV diagnosis improved 1 year viral load suppression and survival (23,24). Screening and pre-emptive treatment for cryptococcal infection combined with a short initial period of adherence support after initiation of ART decreased mortality from 18% to 13% in people with advanced HIV disease in Tanzania and Zambia (25). A trial of enhanced prophylaxis for opportunistic infections at the time of ART initiation in people with advanced HIV disease in multiple African countries decreased mortality from 12.2% to 8.9% (26). These trials all recruited **ART naïve** participants from **outpatient clinics**.

Our research has identified **hospitalized** HIV-infected patients in Africa who are **discharged home** as an extremely high mortality group, in need of tailored services to improve survival. Approximately one-third of these patients have previously defaulted from ART and two-thirds are ART naïve. There have been **no randomized trials** of interventions targeting this group in Africa, and very few globally (27,28). Our pilot data from Mwanza, Tanzania and studies from South Africa suggest a one-year mortality rate for these discharged patients **≥ 25%** (11–14,16)**.** The major lesion is **poor linkage** during the transition from hospital to outpatient HIV clinic care. In Mwanza Tanzania, only **63%** of HIV-infected patients discharged from the hospital attended the HIV clinic within one-month, and failure to attend the clinic was strongly predictive of death (14).

Our preliminary research in Tanzania demonstrates that the psycho-social factors leading to poor linkage are multiple, complex, but surmountable. They include unemployment, traditional health beliefs, low self-efficacy, lack of transportation, lack of social support, stigma, low perceived need for HIV care, and physical weakness. Lack of social support and low self-efficacy were the most commonly cited factors. To address these factors, we adapted the Anti-Retroviral Treatment and Access to Services (**ARTAS**) intervention, which has been demonstrated in the United States to improve linkage to medical care in persons recently diagnosed with HIV. We call the adapted intervention DARAJA (BRIDGE). It is an individual-level time-limited five-session social worker intervention with the goal of linking hospitalized HIV-infected patients to outpatient HIV care upon discharge. A pilot of DARAJA in 31 HIV-infected patients at Bugando Medical Center (BMC) in Mwanza Tanzania showed that **linkage** improved from **63% to 100%** and **survival** from **75% to 90%** when compared to historical controls **(see preliminary results).**

We propose a randomized controlled trial of the DARAJA social worker intervention versus current standard of care in **500** HIV-infected adults consecutively discharged from study hospitals in Mwanza, Tanzania. The primary endpoint is survival at one year. The trial will be conducted by an experienced team of investigators from the Mwanza Interventional Trials Unit (MITU), Weill Cornell Medicine, and the London School of Hygiene and Tropical Medicine, who have a long track-record of productive research collaboration. The trial responds to the WHO and NIH calls for research on differentiated models of care for HIV-infected populations at high risk of death (**PA-17-182**). The proposed study is also supported by the Director of the Bugando Medical Center and the Regional Medical Officer for the city of Mwanza **(see letters of support).**
Upon successful completion of the trial, the Tanzanian Ministry of Health enthusiastically supports large scale implementation trials and cost-effectiveness studies of the DARAJA intervention **(see letter of support).** The proposed research has the potential to significantly improve survival of hundreds of thousands of HIV-infected patients in Tanzania and other African countries.

B. INNOVATION:

- We have identified **hospitalized HIV-infected patients** who are being **discharged home** as an understudied population with mortality **≥ 25%** in the one year following discharge. Interventions to improve survival that are tailored to the needs of these patients are urgently needed. There have been no trials addressing the needs of this population in Africa.
- We have identified the transition between the hospital and the outpatient HIV care clinic as a **critical lesion in the HIV care continuum**.
- We propose an innovative social worker intervention which creates a **seamless bridge** between the hospital and the clinic. The intervention was adapted from the ARTAS intervention which has been shown effective in the United States and in the outpatient setting in Africa. A model intervention to facilitate the transition from the hospital to the clinic does not currently exist in

Tanzania or in other African countries.

- We propose to study **both ART naïve and ART defaulters**. Recent clinical trials of differentiated models of care in Africa have focused upon ART naïve patients and excluded people with a prior ART history. We believe including both groups reflects the reality faced by hospital clinicians in Tanzania.
- We utilize **social workers** in our model intervention because they are a recognized cadre of health care professionals in Tanzania and are responsible for helping hospital patients access social services. Other types of health care workers (nurses, peer educators) could be utilized in other settings depending upon availability and local context.
- We recognize the hospitalization of HIV-infected adults in Africa as a unique **opportunity** to initiate and maintain life-saving HIV care in an easily identified, temporarily "captive", and high mortality group.

C. APPROACH

This is divided into two sections: Background and Preliminary Studies (C.1.) and Research Strategy (C.2.)

C.1. Background and Preliminary Studies: Tanzania is the largest country in East Africa (population 55,572,000) and one of the 30 poorest countries in the world (29). In Tanzania, 44% of the population lives below the poverty line of $1.25 per day (30). We propose an intervention in Mwanza, the 2nd largest city in Tanzania with a population of 819,000 (31) (**Figure 1**).

Figure 1. Map of Tanzania and Mwanza

The HIV epidemic in Tanzania: The HIV prevalence in Tanzania is 4.7%. There are ~2.6 million Tanzanians currently living with HIV (29,32). HIV is the leading cause of **hospital admissions and death** in adults in Tanzania (33). In 2016, HIV caused 18% of all adult deaths (33,000) (22,33). We conducted studies on the prevalence of HIV infection in hospitalized patients at the Bugando Medical Center in Mwanza, Tanzania. Bugando is the major public hospital in Mwanza and provides 75% of all the in-patient and outpatient HIV care in the city. We documented that 2,393 **(22%)** of 11,045 hospitalized adults were HIV-infected (1). HIV **prevalence rates among hospitalized adults** in other sub-Saharan hospitals are similar, ranging from **22% to 60%.** These rates have not decreased in recent years (1–10). The in-hospital mortality of HIV-infected adults in Tanzania and other African countries ranges from 20-35% (1,4,10,14,34,35).

There is a **very high mortality rate** in HIV-infected adults in the **first 12 months after discharge** in Tanzania. We conducted a study of 172 HIV-infected adults consecutively admitted to the Bugando Medical Center in Mwanza in 2013 (14). Details of their HIV status and ART history are provided in **Table 1**. Of note, the median time on ART in the 60 people who defaulted in the past was **only 45 days**. The median age of the HIV-1 infected adults was 37 years and 45 (26%) died in the hospital. The 127 survivors were discharged an average of 7 days after admission and were referred to HIV clinics.

Table 1: HIV and ART History of 172 HIV infected Patients Admitted to Bugando Medical Center*

New HIV Diagnosis	38 (22%)
Prior HIV Diagnosis	
ART never started	68 (40%)
ART default	60 (35%)
On ART at hospital admission	6 (3%)

* patients consecutively admitted Sept- Dec 2013

Of the 127 patients, only 80 **(63%)** attended an outpatient HIV clinic visit in the first month and only **76 (60%)** were alive at 12 months. Among patients who survived at least one month, those who **failed to link** to the HIV clinic within one month were **5.8 times more likely to die** in the first year than those who did attend. **Other studies from Africa** have demonstrated post- hospital 1-year survival rates of only **50-75%** (11–13,16).

Current Standard of HIV Care in Mwanza: We have implemented procedures to improve care for hospitalized HIV-infected patients following WHO guidelines. Of note, the PI of this proposal, Dr. Robert Peck is an attending physician on the adult medical wards of Bugando Medical Center, and he spearheaded these improvements (14,36–41). We have expedited ART initiation following WHO guidelines, implemented routine screening and prophylaxis for TB and cryptococcus, and improved discharge planning for clinic linkage. A hospital nurse provides discharge counseling, and on the day of discharge, she accompanies patients to the HIV clinic and helps to make a clinic appointment within one-week. She also calls by cell phone the night before to remind patients to keep their clinic appointment.

HIV clinic services are provided **free-of-charge** in Mwanza including physician services, nursing care, diagnostic testing, and medications. The clinic is staffed by 5 physicians, 12 nurses, 3 data entry clerks, and 2 peer educators. In the first month at the clinic, patients are seen **weekly;** thereafter visits are monthly. Monthly HIV clinic visits include monitoring for new symptoms and assessment for medication toxicity. **One-month medication refills** are provided for the first year and every 3 months thereafter if the patient is doing well. As part of routine clinic services, plasma HIV viral load testing is performed at 6 and 12 months. Patients with a plasma HIV RNA level >1,000 copies/μl undergo intensive counseling with development of an individualized adherence plan. Repeat testing is performed after 3 months. HIV resistance testing is not available in Mwanza.

All clinical, laboratory and pharmacy information is routinely entered by HIV clinic staff into a standardized, national **HIV Clinic** electronic medical record (**EMR**) system. Pharmacy records including number and date of all antiretroviral drugs dispensed. All clinical data including demographics, contact information, HIV diagnoses, WHO stage, tuberculosis history, and physical exam findings are entered. Laboratory results including HIV viral load tests, CD4 T cell counts, and tests for TB, hepatitis and STIs are also entered into the EMR. The EMR database has been utilized by members of our study team in numerous studies and the quality of the data is excellent (42–44) (See Facilities and Other Resources for details).

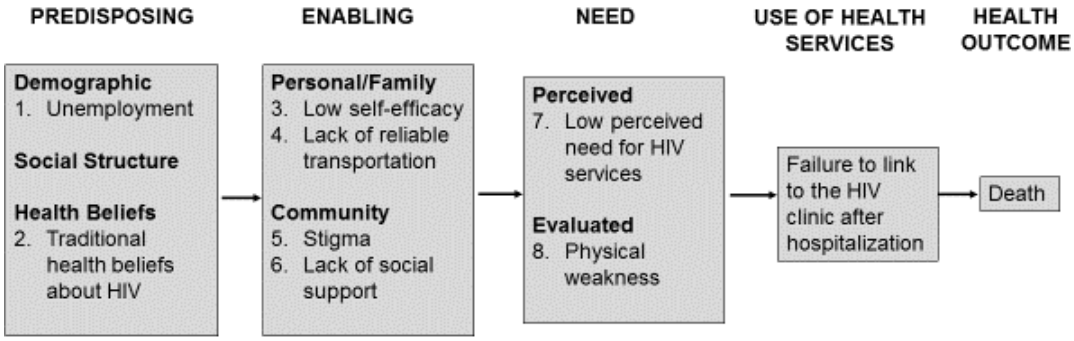
Our experience is that all hospitalized patients at Bugando Medical Center meet the criteria for advanced HIV disease. **Two-thirds of hospitalized patients start ART** in the hospital. The remaining one-third start ART within 4 weeks due to complicating conditions such as cryptococcal meningitis or tuberculosis. These changes in the standard of care have led to **incremental improvements** in rates of post-hospital linkage and survival but ~30% of patients still fail to link to primary care within 1 month and only 75% survive for 1 year. In the only published report of initiating rapid ART for hospitalized patients in Africa, the survival was also **75%** (16).

Qualitative studies on factors influencing post-hospital linkage to the HIV clinic: We conducted semi-structured qualitative **interviews** and **focus groups** with thirty HIV-infected Tanzanian adults recently discharged from the Bugando Medical Center and ten healthcare workers involved in HIV care (3 HIV clinic MDs, 2 HIV clinic nurses, 2 ward nurses, 2 ward MDs and 1 community health worker). Transcripts were analyzed using a grounded theory by two reviewers, and common themes identified. The **Gelberg and Andersen Behavioral Model of Health Care Utilization for Vulnerable Populations** was the conceptual framework for organizing factors that influence linkage to the HIV clinic (17–19,45). Multiple studies have used the model to evaluate the use of health services among HIV-infected populations and to develop interventions to improve outcomes (20,45–48). The model emphasizes 3 domains which operate together to predict service utilization: *predisposing characteristics*, *enabling resources*, and *need* (17,49).

Predisposing characteristics identified in our interviews included **unemployment**: "*I was too sick to work. When I started regaining my strength, I did not have time to take care of my health because I spent all of my time trying to find another job.*" **Traditional health beliefs:** *"When the doctor first told me that I had HIV I did not believe him. I thought I was bewitched by a relative. I attended traditional healers for a year before finally deciding to go to clinic."* According to the model, the **enabling factors** are generally the most mutable (17). We identified four important enabling factors for our population. **Low self-efficacy:** "*After I was discharged from the hospital I did not attend the HIV clinic because I was stressed and overwhelmed with my new diagnosis of HIV and I had heard that the HIV clinic was complicated*." **Lack of reliable transportation**: "*I missed many appointments after my diagnosis because I could not find transportation to the HIV clinic"*. **Stigma**: "*I couldn't attend my HIV clinic appointments because I didn't have permission to leave my boarding school and I didn't want to tell my teacher about my HIV status."* **Lack of social support**: "*When my husband found out I had HIV, he took everything and disappeared. The rest of my family refused to help. I cared for my 10-year old*

child alone." We identified two needs: **Low perceived need for HIV services**: *"The greatest challenge is that many hospitalized HIV-infected patients don't yet fully understand the importance of receiving lifelong treatment for HIV."* **Too weak to visit clinic**: *"I missed several clinic appointments after being discharged from the hospital because I was too weak to stand and walk from my bed to the door of the house."* Of note, factors **most commonly reported** by HIV-infected patients were **lack of social support** (23/30) and **low-self efficacy** (21/30). Our adapted **Gelberg and Andersen Model** includes these **8 factors** associated with failure to link to the HIV clinic (**Figure 2)**.

Figure 2.
Factors Influencing Linkage to the HIV Clinic after Hospitalization in Tanzania



Adapted from Gelberg et al. Health Serv Res. 2000;34(6):1273-1302.

Developing a new model of care to improve linkage to the outpatient HIV clinic: We adapted the Antiretroviral Treatment and Access to Services (ARTAS) intervention for use in Tanzania. ARTAS is a **5-session, social worker intervention** aimed at linking HIV-positive individuals to primary care services (50). The social worker helps patients to identify the critical barriers that may prevent them from linking to HIV care and helps them access the social and health care system. It is well suited to helping people navigate a fragmented, low-resource health system and overcome barriers stemming from extreme poverty and heightened HIV stigmatization. Participants are encouraged to identify and use their **own strengths, abilities, and resources** to solve problems and overcome barriers. This approach borrows heavily from theories of **empowerment and self-efficacy** (51).

In a 2005 randomized clinical trial of ARTAS in the United States, 316 adults recently diagnosed with HIV infection were randomized to the intervention or standard referral to an HIV clinic (47). After 6 months of follow up, 78% of participants in the intervention arm had linked to primary care compared to 60% in the control arm (p=0.0005). The investigators validated their findings in an implementation trial at 10 sites across the United States (20). Based on these results, the US Centers for Disease Control recommended ARTAS as an evidence-based intervention to increase linkage to HIV primary care (50). Of note, a recent study in **outpatients** in South Africa also demonstrated that ARTAS, implemented by social workers, improved linkage to HIV clinical care (52). **Dr. Lisa R. Metsch,** who has joined our team as a study consultant, participated in the development and implementation of the original ARTAS intervention (20,47,48,27). She assisted the Tanzanian team in adapting this intervention for hospitalized patients in Africa.

In Kiswahili we call the intervention **DARAJA (BRIDGE**) since the social worker bridges the divide between the hospital and the HIV clinic. DARAJA consists of **5 sessions** with a social worker over a **3-month period**. The first session occurs in the hospital and the second session occurs in the patient's home. Other sessions occur either in the home of the patient or at the HIV clinic. The 1st session consists of building trust and identifying the patient's strengths, needs, and barriers to accessing medical care. The 2nd and 3rd session focus on goal setting and identification of specific actions that are necessary for the patient to overcome barriers to HIV clinic attendance. The 4th session consists of a structured review process **emphasizing the patient's strengths**. The 5th session focuses on transitioning social worker responsibilities to the patient's HIV primary care clinic team. During sessions 2, 3, 4 and 5, the social worker may accompany the patient to clinic appointments. Social workers are also available by phone or in person from 9-5 PM Monday–Friday to speak with patients if they seek help. In addition, the social worker also makes **weekly phone calls** to each participant to remind them of clinic appointments and to respond to questions or concerns.

We designed our intervention to address the eight factors identified in the Gelberg and Andersen Model and other factors that may arise. The social worker reviews the eight previously identified factors with the patient. Most patients report a combination of ~ 3 of these factors as the main barriers to attending HIV clinic. The social worker communicates with hospital nurses and doctors to fully understand the discharge instructions and with the HIV clinic staff to assure that there is a seamless transition between the two.

Pilot Study of DARAJA Social Worker Intervention: In 2016, we enrolled 31 consecutive HIV-infected adults on the wards of the Bugando Medical Center. The median age was 38 years, 65% were female and the median $CD4^+$ T-cell count was 193 [79-271] cells / mm^3. We included patients who were ART naïve (n=20) and ART defaulters (n=11). We did not include 2 patients who were on ART on hospital admission and were already linked to the HIV clinic. ART was initiated according to the WHO guidelines for people with advanced HIV disease. Twenty participants (65%) were started on ART while still in the hospital. The remaining 11 had mitigating conditions (cryptococcal disease, TB) and were started within 1 month. A single social worker performed the intervention as described above. The total time spent on all five sessions with each patient was 6-8 hours per participant, similar to previous reports (20,47).

All 31 (**100%**) of the study participants attended the HIV clinic in the first month after hospital discharge. Twenty-eight out of 31 (**90%**) **were alive at 1 year**. The social worker recorded observations throughout the course of the pilot study of how the intervention enabled participants to link to HIV primary care. **Table 2** lists the eight factors from our adapted Gelberg and Andersen Model and strategies the social worker used to overcome them. Study participants reported **no loss of confidentiality or social harms**. Many participants stated that the social worker's assistance was critical for their linkage to HIV care. One participant stated, **"I would have been lost along the way if you had not been with me."**

Table 2
Factors and Strategies to Improve Linkage to HIV Clinic Care

Factor	Strategies
Unemployment	Connect patient with the hospital's Social Welfare office Meet with former employer to discuss re-employment
Traditional health beliefs	Explain that traditional medicine and HIV care are complementary not exclusive Facilitate open dialogue about traditional healers and herbal medicines
Low self-efficacy	Help patients to develop a specific action plan for linking to care Attend clinic visits with participant to develop confidence
Lack of reliable transportation	Introduce participant to Social Welfare Office which provides transport voucher Identify other resources for transportation (friends, neighbors, church)
Stigma	Skill building with role play to overcome individual level stigma Link participant with HIV support groups
Low perceived personal need for HIV services	Reinforce that participants can live a long and productive life with ART Link with HIV peer educators at clinic
Physical weakness	Assist severely ill participants with requesting and receiving home based care Identify family members or neighbor who can accompany patient to clinic

C.3. RESEARCH STRATEGY

Overview of the Study: We will conduct a randomized controlled trial to evaluate the efficacy of a social worker intervention in **500** HIV-infected adults who have been hospitalized at hospitals in Mwanza region such as Bugando Medical Center, Sekou Toure Regional Referral Hospital, Buzuruga Health Center and Nyamagana District Hospital, and hospitals in Misungwi, Sengerema and Magu Districts, Tanzania. Participants will be enrolled and randomized 2-3 days prior to hospital discharge. HIV-infected adults randomized to the DARAJA intervention will have **5 sessions** with the social worker over a **3 month period**. The control group will not receive the DARAJA intervention. All other aspects of care in the two groups will be the same and follow current standard practice. The **primary hypothesis** is that the social worker intervention will significantly increase survival at 12 months compared to controls. The study will have > 80% power to detect a difference in the primary study outcome from **75%** to **90%**.

Research leadership team: Weill **Cornell** Medicine, the Mwanza Intervention Trials Unit (**MITU**) and the London School of Hygiene and Tropical Medicine (**LSHTM**) have collaborated since 2008 on research to inform national and international HIV care and prevention. Prior research includes a cluster-randomized trial of a school based intervention to reduce sexual risk (53); a randomized trial demonstrating how educating religious leaders increased rates of circumcision for HIV prevention (54); and a cluster-randomized trial of a multi-component health systems intervention to improve primary care services for chronic diseases (55–58).

Dr. Robert Peck (PI) has been living and working in Tanzania since 2007 and established the initial collaboration between Cornell, MITU and LSHTM. He is an attending physician of internal medicine at Bugando Medical Center and led the DARAJA pilot study described above in **C.1. Dr. Saidi Kapiga (Tanzania Site PI)** has been the Scientific Director of MITU since its inception and is a faculty member of the LSTHM. He has led numerous clinical trials in Tanzania of social and behavioral interventions to increase survival in HIV-infected adults. **Dr. Heiner Grosskurth**, a LSHTM faculty member based at MITU, is a leading authority in health systems interventions in Africa. **Dr. Daniel Fitzgerald** has been working with Dr. Peck since 2001 and is an expert in clinical trials of interventions to improve survival of HIV-infected people in developing countries. **Dr. Lisa Metsch** is a social scientist and co-developer of the ARTAS intervention. **Dr. Elialilia Okello**, a sociologist and medical anthropologist with extensive experience in Africa, will work closely with Dr. Metsch to oversee the qualitative research in Tanzania. **Dr. Bruce Schackman** is a leading expert in health economics who has conducted extensive research in both the US and developing countries. **Dr. Sean Murphy** and **Dr. Myung Hee Lee** provide expertise in economic and statistical analysis.

Of note, Dr. Fitzgerald and Dr. Kapiga are Dr. Peck's US and Tanzanian mentors (respectively) on his K01 international research training award. This research addressed hypertension and cardiovascular disease in HIV-infected patients in Mwanza, Tanzania. Drs. Grosskurth and Lee are also mentors on Dr. Peck's K award. These established collaborations are an invaluable asset and ensure effective coordination of the proposed research.

Tanzania research implementation team: Dr. Peck (PI) will oversee all aspects of the proposed study and will visit all medical wards and HIV clinics twice weekly to address research protocol questions raised by the ward and clinic staff. He will also meet with the 3 social workers, the research team (research coordinator and 3 research assistants) and the 2 MITU data clerks twice weekly to ensure implementation of all study procedures. He will also meet with the Director of BMC on a monthly basis and will provide quarterly reports to the Tanzania Ministry of Health. A Research Fellow will assist Dr. Peck in all of the above duties. She will compose and disseminate monthly reports regarding study enrollment and follow-up. She will also collect the health economics data.

Dr. Severin Kabakama (Study Coordinator) will visit all the medical wards and HIV clinics multiple times per week. He will meet daily with the social workers, the research team and the MITU data team. He will perform participant randomization. He will immediately report any protocol deviations or participant complaints to Dr. Peck. Dr. Kabakama and Colombe will also participate in data analysis, manuscript preparation and dissemination.

The research assistants based at the medical wards of the study hospitals will identify appropriate study participants, obtain informed consent, and conduct the enrollment study questionnaire. Each research

assistant will subsequently follow their assigned study participants until the end of the study. The research assistants will conduct the 3, 6, 9, 15, 18 and 21-month phone calls as well as the 12 and 24-month study visits and will enter data onto tablets. Participants who are lost to follow up at any study visit will be identified by the research assistant, who will work with field workers to track the participant in the community.

The MITU data entry clerks will visit all HIV clinics weekly to extract data from the HIV EMR and to transfer this data to the MITU database. The MITU data clerks will also upload data provided by the research assistants. They will provide quality control to all data and will report any data issues to the research coordinator. They will also be responsible for transferring data from MITU to Cornell for data analysis. The 2 MITU data clerks will be assisted by the quality control data field staff. This field staff person will be responsible for the accuracy of data entry into the HIV Clinic EMR and for tracking any missing HIV PCR results. The Qualitative Research Assistant) will conduct the qualitative interviews of study participants and health care workers during Years 4 and 5 of the study and will assist in qualitative data analysis.

The DARAJA intervention will be provided by a team of three social workers. **Kelvin Abel**, who was the social worker for our pilot, will train and lead the team. Drs. Peck and Metsch will assist in this training in the DARAJA intervention. One social worker will be assigned to each medical ward.

Study Site: We will enroll from hospitals in Mwanza region, including Bugando Medical Center, Sekou Toure Regional Referral Hospital, Buzuruga Health Center and Nyamagana District Hospital, and hospitals in Misungwi, Sengerema and Magu Districts. **The Bugando Medical Center** is the main public hospital in the city of Mwanza, Tanzania. It has 800 beds and 3 adult medicine wards with 50 beds each (150 total). On average, 210 adults are admitted every month in the male and female medical wards, amongst them, 23 are HIV seropositive. **Sekou Toure Regional Referral Hospital** has 375 beds and on average admits 47 patients per month in the medical wards, of whom 18 are HIV+. **Nyamagana District Hospital** has 88 beds, but attends to female patients only. It admits an average of 71 female patients per month, 11 of whom are HIV+. **Buzuruga Health Centre** has 20 beds, but attends to female patients only. It admits 40 patients per month on average of whom 5 are HIV+. All these health facilities have recognized HIV care clinics at which antiretroviral therapy is being provided and monitored. Other study sites include Misungwi, and Magu and Sengerema District Hospitals. Each of these facilities has 150 bed capacity, with an average daily occupance of 60 – 80 patients.

All patients admitted to the adult medical wards undergo assessment for HIV (1,14,40), in accordance with Tanzanian National Guidelines for HIV (59). For those with previously documented HIV infection, the diagnosis is confirmed by retrieval of the test result from the HIV EMR. For patients not previously tested, the hospital nurses provides voluntary counseling and testing for HIV with bedside rapid antibody tests. The medical wards discharge ~40 HIV- infected adults per month (1,14,40). Approximately 75% of the HIV-infected patients live in Mwanza and are referred to the BMC outpatient HIV Clinic which is on the first floor of BMC.

Study Population, Inclusion and Exclusion Criteria: All HIV-infected adults hospitalized in study health facilities in Mwanza during the enrollment period will be screened for eligibility. We will include newly diagnosed HIV-infected patients, ART naïve patients reengaging in care, and patients who received ART previously but defaulted. **Inclusion Criteria:** 18 years of age or older; HIV-infected; lives in the city of Mwanza; will be referred to a clinic inside the city of Mwanza; antiretroviral naïve or defaulted for > 7 days; has mobile phone or access to mobile phone; planning to stay in Mwanza region for the next 24 months; able to speak Kiswahili or English; capable and willing to provide informed consent; willing to provide locator information and 2 designated contact persons; willing to have a home visit from a study team member. **Exclusion Criteria:** pregnant; on ART at hospital admission.

Recruitment and Informed Consent: We will recruit from the medical wards of health facilities in Mwanza region**.** The median length of hospital stay is 6 days (interquartile range: 4-10 days) (1,14). Hospital physicians begin discharge procedures 2-3 days before the anticipated date of discharge. A **research assistant** will be assigned to each of the medical wards and will ask the medical team each day if there are patients eligible for enrollment. The research assistant is a staff member independent of the clinical team and does not participate in patient care. The research assistant will ask if the patient is interested, complete a **study eligibility checklist** and initiate **informed consent**. Patients who do not provide consent will continue to receive free hospital and HIV clinic services. We will document the number screened and the reasons for study exclusion.

Study Enrollment, Randomization, and Study Intervention: The baseline questionnaires will be completed on the day prior to discharge. We will consecutively enroll 25-30 participants per month until we reach a sample size of 500 participants (18-month enrollment period). The research assistant will assign a unique study identification number to each participant, collect demographic and clinical data from the medical file, and administer a baseline questionnaire. Locator information will be obtained for the study participant and 2 designated contact persons. The designated contact persons will be friends or relatives who the research team can contact if the study participant is not available for a study visit. Our own work and the work of others has demonstrated that phone calls and messages are highly acceptable and effective as a means of communication with HIV-infected patients in East Africa (14,60). Cell phones are the primary means of communication in Tanzania, and >95% of patients or their families use phones.

After this baseline assessment, on the morning of hospital discharge, participants will be randomized to either the DARAJA social worker intervention or the control group in a 1:1 ratio using a computer generated random assignment. The **research coordinator**, **Dr. Severin Kabakama**, will provide the computer generated random assignments to Mr. Abel, the chief social worker, and the social worker assigned to the ward will see the participant for the first time in the hospital on the morning of discharge. The participant will be considered enrolled once randomization occurs.

All 500 participants in the trial will receive care according to current standard practice in Mwanza, which was described previously (**see section C.1. Current Standard of HIV Care in Mwanza)**. In brief, ART is initiated in the hospital according to the WHO guidelines (15). For a subset of patients with TB or cryptococcal disease, ART may be deferred for 2 to 4 weeks to prevent immune complications. All HIV-infected adults receive a 30-minute counseling session before hospital discharge by a hospital nurse trained in HIV care. They receive detailed instructions regarding their medications and clinic appointments. Upon discharge, the hospital nurse escorts patients to the HIV clinic and helps them schedule an appointment within one week. The hospital nurse also takes the phone number of patients and calls them the night before their scheduled visit to encourage them to go to clinic.

The **250** participants randomized to the DARAJA intervention group will meet with a social worker in the hospital on the morning of discharge as described previously **(see C.1 Pilot Study of DARAJA Social Worker Intervention)**. The second visit will be in the home, and then there will be three subsequent visits either in the patient's home or in the outpatient HIV clinic during the ensuing 3 months (total of 5 social worker visits). Of note, the social worker will be blinded to those participants enrolled in the control group.

Research Schedule, Measures, and Outcomes: A research schedule with the timing of study visits, measures, and outcomes for all 500 participants is provided in **Table 3** on the next page. These are in addition to the routine care or DARAJA social worker visits. All 500 participants in both study groups (control and DARAJA) will have three face-to-face visits and six phone interviews with a research assistant over 24 months. The **enrollment**,**12 month**, and **24-month** visits will be **face-to-face**. At 3-month interval phone calls, the research assistant will interview the participant about health status, clinical visits, and psycho social factors. The data managers will also extract information on clinic attendance, medications, and laboratory studies from the HIV Clinic EMR every three months. We will continue follow-up for 24 months to measure sustainability of the intervention. A description of the primary and secondary outcomes for each of the study aims is provided below:

Survival: Deaths will be documented by four methods. **1)** If a study participant misses a visit or does not respond to a phone call, then the research assistant will telephone the contacts and inquire about the participant's status. **2**) If neither the study participant nor the designated contact persons are available, a home visit will be made by a field worker. **3)** If the family reports that the participant was hospitalized, we will review hospital records. **4)** Tanzania has a well-organized system for death certificates, and nearly 100% of people who die in Mwanza have a death certificate. We will obtain copies of death certificates for all participants who cannot be contacted or who are reported deceased by a family member. The final cause of death will be decided by an adjudication committee consisting of the PI, Dr. Saidi Kapiga and Dr. Daniel Fitzgerald.

Linkage and other steps in the HIV care continuum: Linkage will be defined as having at least one visit to the outpatient HIV clinic. Twelve-month retention will be defined as being alive and having a clinic visit between 11 and 13 months. Twenty-four-month retention will be alive with a visit between 23 and 25 months. Adherence will be measured with a 3-day recall questionnaire and by reviewing pharmacy refill records and calculating the proportion of prescribed days of ART which are actually picked up over time. HIV RNA levels are measured routinely at the Mwanza HIV clinic at 6, 12 and 24 months, and we will retrieve results from the EMR. HIV viral suppression will be defined as a plasma HIV RNA level <1,000 copies/μl (15). Participants who have ≥1,000 copies/μl or who do not have plasma HIV RNA level measured will be considered **virologic failures.**

TABLE 3.
RESEARCH SCHEDULE, MEASURES, AND OUTCOMES

		Month of Research Visits								
RESEARCH ASSISTANT COMMUNICATIONS		**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
Face-to-face visits		X				X				X
Phone call			X	X	X		X	X	X	
DEMOGRAPHICS										
Age, sex, education	*	X								
Economic status (weekly income)	*	X				X				X
MEDICAL HISTORY										
Date of HIV diagnosis	+	X								
Prior ART use	+	X								
WHO stage	+	X	X	X	X	X	X	X	X	X
Physical measures (height, weight, blood pressure)	+	X				X				X
Alcohol use (AUDIT) (65,67,68)	*	X				X				X
Depression (PHQ-9) (64)	*	X				X				X
PSYCHOSOCIAL FACTORS										
Employment (ARTAS Baseline and Follow-up Tools) (69)	*	X				X				X
Traditional health beliefs (HIV Knowledge Questionnaire) (70,62)	*	X				X				X
Self-efficacy (HIV – Adherence Self-Efficacy Scale) (71)	*	X				X				X
Transportation (ARTAS Baseline and Follow-up Tools) (69)	*	X				X				X
Stigma (AIDS-Related Stigma Scale) (72,73)	*	X				X				X
Social support (SPS-10) (63)	*	X				X				X
Perceived need for HIV services (ARV Medications Attitude Scale – 15) (74)	*	X				X				X
Physical Weakness (SF-12) (75,66)	*	X				X				X
PRIMARY OUTCOME										
Death	¢		X	X	X	X	X	X	X	X
STEPS IN HIV CARE CONTINUUM										
Linkage to HIV clinic (date of first clinic visit)	+		X	X	X	X	X	X	X	X
Retention (attendance at monthly clinic visit)	+		X	X	X	X	X	X	X	X
ART adherence (3-day recall; pharmacy refills)	*+	X	X	X	X	X	X	X	X	X
Plasma HIV-1 RNA level		X		X		X				X
ACCEPTABILITY										
Qualitative interviews	§						X	X	X	
COST										
Number and type of health facility visits	*+	X	X	X	X	X	X	X	X	X
Laboratory or radiologic services utilized	*+	X	X	X	X	X	X	X	X	X
Medications use (prescription, non-prescription, and herbal)	*+	X	X	X	X	X	X	X	X	X
Staff time for social worker Intervention	$	X	X	X	X	X	X	X	X	X

***** Research assistant administered questionnaire
+ Data abstract from the HIV Clinic EMR
¢ Deaths will be documented by phone calls, home visits, hospital records, and death certificates
$ Timing of a subset of social worker visits; social workers will also log all time spent on intervention activities
§ Qualitative interviews conducted with a subset of study participants and health care workers

Factors from the Gelberg and Andersen Model: We will measure the eight factors of the Gelberg and Andersen Behavioral Model of Health Services Utilization for Vulnerable Populations at enrollment, 3 months, 12 months, and 24 months (18). The measurement tools are listed in Table 3 and have been translated into Kiswahili and used in prior studies in East Africa (61–66).

Acceptability and Barriers/Facilitators of Linkage: This will be assessed using **qualitative interviews** conducted at **12 months** after study enrollment with a subset of **20 intervention participants** and **20 standard care control participants** and **20 healthcare workers** (nurses and physicians). Dr. Elialilia Okello and a trained qualitative research assistant will conduct the interviews to explore factors influencing linkage to HIV primary care and ART initiation. We will also seek to interview all participants who are **alive but not in HIV primary care at 24 months** to understand reasons for non-linkage. The interview guide will be developed, pretested, and will address the following topics: **1)** participant's experience with the intervention or standard of care (e.g., usefulness of the intervention, beliefs (and misbeliefs) and concerns about the intervention, experience with the services offered in the experimental or the control group); **2)** contextual-level topics such as living conditions, other health problems such as mental health, and personal resources (work, housing, finances, education, social support, health services access and utilization); and **3)** any change in risk behavior and contextual factors involved. Participants will receive $10 for travel and their time in interview participation. In addition, the 20 health care workers (nurses and physicians) will be asked to assess implementation challenges, unintended consequences, and provider acceptability. Interviews will be approximately 30- 45 minutes and conducted in Kiswahili, audio-recorded, transcribed verbatim, and translated in English for analysis. These data will inform how and why certain aspects of the intervention were effective or ineffective and also inform future adaptation and scalability of the intervention.

Cost: Healthcare utilization data will be collected from the EMR, including attendance at HIV and other care visits in both study arms, laboratory services, and medications. Participants will also be interviewed by the research assistant at 3-month intervals to obtain information about their use of health services at non-study sites such as hospitalizations or visits to other medical specialists. Staff time will be determined by Dr. Soledad Colombe observing a sample of sessions to record time of the social workers. These data will be used to estimate costs.

Data Management: All data will be collected using an Android tablet and will be stored on encrypted servers at MITU. Research assistants will complete research questionnaires on the tablets at each visit. They will abstract clinical and laboratory information from the HIV Clinic EMR at each study visit and enter the data onto Case Report Forms (CRFs) on tablets. Individuals will be identified by a study ID number and no participant identifying information (name, address) will be recorded on questionnaires or CRFs. The MITU data manager (Mr. Ramadhan Hashim) will supervise and clean all data and will transfer the data into the NIH approved **REDcap** data management system. The REDcap system is encrypted and password protected and has been used in prior Cornell-MITU NIH supported research.

Quality Control and Assurance: The PI and Dr. Saidi Kapiga will oversee data quality control and assurance. They will review all informed consent documents and study eligibility checklist forms. The PI, Dr. Kabakama and Mr. Hashim will review the REDcap data files for internal validity and completeness and send queries to the data management team in Tanzania each week. The team will respond to queries within one week. Prior to enrollment, the research coordinator and research assistants will verify that the completion of the informed consent form and that all inclusion and exclusion criteria have been met. During the trial, all data collection documents will be verified by the research coordinator. Additionally, the REDCap system for data collection will also perform quality control checks to ensure that all required information are obtained.

Sample Size and Power: We performed sample size (N)/power calculation using the log-rank test for the primary outcome (**survival**) in the two independent study groups. With 500 participants and 10% lost to follow up, we have >80% power with α of 0.05 to detect a 10% to 20% absolute difference in survival between the DARAJA intervention group and the control group across the range of expected survival rates (**Table 4**). We will have 98% power to detect a difference between 75% vs. 90% per our primary hypothesis. This is shown in *italics* in Table 3. Our sample size will also provide reasonable power for important secondary analyses. For example, for secondary aim 1, we will have >80% power to detect most 10% absolute differences for linkage and other steps in the HIV care continuum.

Survival Rates DARAJA vs. Control	Absolute Difference	Power (α = .05)
95% vs. 75%	20%	0.99
90% vs. 75%	*15%*	*0.98*
90% vs. 80%	10%	0.87
85% vs. 75%	10%	0.80

Table 4.Power for Different Survival Rate

Data Analysis:

Primary Aim: Survival at 12 months. We will compare survival between the study and control arms using the log-rank test following the intention-to-treat principle. Survival times are measured in days from the date of randomization which will occur on the morning of hospital discharge. This is an individual randomized trial, and we anticipate the two arms will have similar baseline characteristics. Therefore, the primary analysis will be done without adjusting for baseline variables. Since we have one primary outcome, we will test the primary hypothesis without multiple testing adjustments. Statistical tests will be two-tailed, with a significance level of 0.05. If some variables at baseline are notably imbalanced, we will conduct adjusted analyses as secondary or sensitivity analysis using multivariable-adjusted Cox regression and Cochran–Mantel–Haenszel statistics. The results will be summarized in terms of survival rates as well as hazards ratios, along with confidence interval and statistical significance.

Secondary Aim 1: Linkage and other steps in the HIV Care Continuum. Time to linkage will be measured in days from the date of randomization to the first HIV clinic visit. For participants without linkage, follow up time will be censored at the date of lost-to-follow up, death, or study end, whichever happens first. Time to linkage will be compared between groups using the log-rank test. We will conduct adjusted analyses using Cox regression. HIV clinic retention, ART adherence and viral suppression will be treated as binary outcomes at 12 and 24 months. We will compare these outcomes between study arms using the Fisher exact test. We will conduct adjusted analyses using multivariable-adjusted logistic regression and Cochran–Mantel–Haenszel statistics.

Secondary Aim 2: Gelberg and Andersen Model. The factors in the Gelberg and Andersen Healthcare Utilization Model for Vulnerable Populations will be evaluated using **structural equation modeling** (SEM) to take into account modeling of interactions, nonlinearities, and correlated independent variables. A priori, we will create a path analysis of direct and indirect pathways in the Gelberg and Andersen Model domains of predisposing, enabling and need variables. Our model selection will be guided by Information criteria (e.g., AIC/BIC) along with methods for addressing model selection uncertainty provided in Preacher and Merkle (76). We will evaluate the effect of randomization arm upon factors and pathways associated with the primary outcome (survival) as well as secondary outcomes (linkage to HIV clinic). We will also perform **mediation analysis** to determine which factors from the Model act as mediators and moderators of the primary and secondary outcomes, allowing us to explore how and for whom the intervention worked. Short and longer mediation pathways will be tested such as the direct effect of increased self-efficacy on early linkage vs. the effect of increased self-efficacy leading to early linkage leading to survival. Moderation analysis will be conducted to identify (or rule out) potential differential intervention effects for selected subgroups such as whether the intervention is more effective in HIV-infected adults who were ART-naive vs. ART-experienced.

Secondary Aim 3: Acceptability and Barriers/Facilitators of Linkage: All qualitative interviews will be transcribed verbatim, translated in English, and then entered into qualitative software (e.g. Atlas-ti) for coding and analysis. A thematic coding scheme will be created following the main points of the interview guide. To ensure inter-rater reliability of 85%, using Cohen's Kappa (k) index, Dr. Elialilia Okello and her assistant will code the first five transcripts independently, and then compare their results, and discuss ambiguities and inadequacies in the coding scheme. Refinements to the coding scheme will be made via discussion between Dr. Okello and the PI. Dr. Okello and her assistant will then code a second set of 5 transcripts, and come together again to compare their results a second time, discuss remaining ambiguities, and achieve consensus in the coding scheme. Based on our previous experience, it is expected that an inter-rater reliability of 75% or

higher will be achieved through these procedures. After this, they will divide the remaining transcripts and code independently. To check for continued inter-rater reliability, they will jointly code transcripts 20, 25, and 30, and compare results. Following the completion of coding, reports will be generated for each of the codes and narratives will be analyzed for emerging themes across transcripts.

Secondary Aim 4: Incremental cost of the intervention and cost per life saved. The economic evaluation will be overseen by Dr. Schackman and Dr. Murphy, with assistance from Soledad Colombe. The analysis will follow established guidelines for conducting economic evaluations, and will be conducted from the perspective of the healthcare sector (77–79). Healthcare service utilization will be summarized for each arm as descriptive counts such as number of HIV care visits, home visits, laboratory tests, medications, and hospitalizations. Unit costs will be determined for each type of service unit by applying labor rates and materials costs available from the study hospital (unpublished data from the *Improving Health Systems for Chronic Diseases* study (Grosskurth (PI)), and other expense costs available from previous studies (80,81). Unit costs will be multiplied by service utilization to calculate healthcare costs. Resources spent on research activities will be excluded. Costs will be reported from the healthcare sector perspective; patient time and transport costs will also be reported separately.

All data will be analyzed under an **intent-to-treat** principle. We will model the person period for each 3-month period where detailed assessments are given to participants (i.e., months 3 and 6), and the subsequent 6-month follow-up period. All analyses will be conducted using a multivariable Generalized Linear Mixed Model (GLMM). The GLMM is an extension of the GLM that allows for the inclusion of random effects. The multivariable aspect of the model is crucial as it allows for the control of factors that are unbalanced between arms because they were not accounted for in the randomization process or may have become unbalanced due to loss to follow-up. The GLMM allows one to choose the most appropriate mean and variance functions according to the fit of the data. Given the differences in mechanisms to generate data, separate multivariable GLMMs will be estimated to predict the mean value for each resource, at each time period, by study arm.

The method of **recycled predictions** will be used to obtain the final predicted mean values, which will then be summed and tested (82). To account for sampling uncertainty in point estimates, the p-values and standard errors will be estimated using nonparametric bootstrapping techniques within the multivariable framework. The difference in costs between the arms from the healthcare perspective will be compared to the observed difference in survival between the arms to calculate incremental cost per life saved. Finally, parametric methods based on parameters obtained from bootstrapping will be used to estimate an acceptability curves, which will illustrate the probability that the intervention is a good value for different willingness-to-pay thresholds (i.e., cost per life saved). These results will inform and serve as the foundation for future large scale implementation and cost-effectiveness studies.

Missing Data: For time to event analysis (survival, cumulative incidence function analysis), missing information in survival time, time to linkage, time to ART will be treated as censored; followup for these observations will be measured from randomization / hospital discharge to their last observed date or last study date whichever is earlier. Missing covariate for Cox analysis will be handled with multiple imputation and Nelson-Aalen estimator will be used (83). For the Health Economics analysis, the GLMM uses all available data for each participant, regardless of whether or not it is complete, making it an ideal statistical procedure for intent-to-treat approaches with data that are missing completely at random or missing at random (84). We will also conduct extensive sensitivity analyses, including missing not at random approaches, to examine the robustness of our outcomes under varying assumptions.

Challenges and solutions: Cross-arm contamination of the intervention will be avoided by ensuring that the social worker is not aware of the hospital patients who have been enrolled in the control arm. HIV-infected patients are not localized in any one area of the medical wards, so the intervention social workers will not know which patients on the wards are eligible for the study (ie HIV-infected). In addition, the intervention social worker will conduct all hospital activities in a private room.

Timeline: The first 6 months of the project will be dedicated to trial preparation activities including IRB approvals, developing the data collection systems, developing the manual of operating procedures, conducting all staff training, and training quality assurance at the hospitals and HIV clinics. **Recruitment will take 18 months**. Follow-up will be continued for 24 months after completion of the recruitment phase. Three months will be allowed for data cleaning and lock after the end of the follow-up period. The final 9 months will be used for collecting final interviews and clinical data and performing statistical analyses.

D. OVERALL GLOBAL IMPACT: We propose a randomized clinical trial to determine the efficacy of a novel social worker intervention to improve survival for HIV-infected patients discharged from a hospital in Tanzania. Improving post-hospital outcomes for HIV-infected adults has the potential to save **hundreds of thousands** of lives in sub-Saharan Africa. The goals of our trial are to demonstrate the efficacy of the intervention, to determine the value of the intervention to increase HIV clinic linkage, to examine the extent to which the variables in the Gelberg and Andersen Model are mediators and moderators of effect and to evaluate acceptability and cost. Upon successful completion of this trial, we will conduct large scale implementation studies with the Tanzanian Ministry of Health.

PROTECTION OF HUMAN SUBJECTS

This Human Subjects Research meets the definition of a clinical trial. We will study an experimental social worker intervention for HIV-infected adults discharged from Mwanza region hospitals, including Bugando Medical Center, Sekou Toure Regional Referral Hospital, Buzuruga Health Center and Nyamagana District Hospital and hospitals in Misungwi, Sengerema and Magu Districts. The social worker intervention is designed to improve linkage to outpatient HIV care and thereby increase the one-year survival of HIV-infected patients discharged from the hospital. A social worker will have initial contact with the HIV-infected patient in the hospital, a second in the home, and then three subsequent visits either in the patient's home or in the outpatient HIV clinic during the ensuing 3 months.

The current standard of care for discharging HIV-infected adults from the hospital includes: a meeting with a hospital nurse to review discharge plans; escort the patient to see the outpatient HIV clinic on the day of discharge; make an appointment at the outpatient HIV clinic within 1 week after discharge; and a nurse calls patients the night before their clinic visit to remind them to attend.

We will conduct a randomized controlled trial of a social worker based intervention (n=250) and control (n=250) in hospitalized HIV-infected adults age ≥18 years in Tanzania. All 500 patients will receive the current Tanzanian standard of care. The primary hypothesis is that the addition of the social worker intervention will improve survival at 12 months compared with controls. The study has >80% power to detect a difference in survival from 75% to 90%. The proposed study protocol will be approved by the Weill Cornell Medicine IRB and Tanzania's National IRB, and all participants will provide written informed consent prior to enrollment.

1. Risks to Human Subjects:
a. Human Subjects Involvement, Characteristics and Design

a.i. Justification of the involvement of human subjects in research: HIV infection continues to be a leading cause of mortality in Tanzania and other sub-Saharan countries and many of these deaths happen after a hospitalization. The hospital is a good place to "capture" people with advanced HIV disease who are in need of antiretroviral therapy and WHO recommended HIV care. Unfortunately, many HIV infected adults who are discharged from the hospital never go to the HIV clinic and do not benefit from life-saving treatment. The goal of the proposed research is to determine the optimal strategy to help hospitalized HIV-infected patients link to the outpatient clinic. Clinical trial evidence of the efficacy of the social worker intervention will allow us to scale the intervention up in Tanzania (see letter of support from **Tanzanian Ministry of Health**). Future

implementation research can demonstrate the cost and effectiveness of the intervention during scale-up.

a.ii Characteristics of subjects: We will enroll 500 HIV-1 infected Tanzanian adults ≥ 18 years of age from the in-patient adult internal medicine wards of hospitals in Mwanza region.

a.iii. Sampling plan, inclusion and exclusion of subjects: We will enroll HIV infected patients in the hospital ~ 2-3 days prior to discharge. **Inclusion Criteria:** 18 years of age or older; HIV infected; lives in Mwanza region; able to speak Kiswahili or English; capable of providing informed consent; willing to provide locator information and 2 designated contact persons. **Exclusion Criteria:** pregnant; on ART at hospital admission and already linked to an HIV clinic; and lives outside of Mwanza.

*a.iv Vulnerable populations: C*hildren under 18 years of age, pregnant women, prisoners, and other vulnerable populations will not be included in the study.

a.v. Procedures for assignment to study groups and details about interventions: Participants will be randomly assigned in a 1:1 ratio to either the social worker intervention or control group using a computer generated randomization list. Randomization will occur on the morning of hospital discharge. We are comparing an experimental social worker intervention to improve linkage to outpatient care versus current standard of care. Of note, all participants will receive medical care following WHO guidelines including screening and preventive medications for tuberculosis, cryptococcus, and other opportunistic infections. For participants diagnosed with cryptococcus or tuberculosis, the timing of ART initiation (or re-initiation) will follow WHO guidelines and may be delayed. For all other participants ART will be initiated within 7 days of HIV diagnosis for those newly diagnosed or within 7 days of hospital admission for those re-engaging in care.

The Social Worker Intervention Group: Patients in this group will receive the "DARAJA" social worker intervention. A social worker will have an initial contact with the HIV-infected patient in the hospital, a second visit in the home, and then three subsequent visits either in the patient's home or in the HIV clinic during the ensuing 3 month (total of 5 social worker visits). The social worker will encourage the patient to use their personal strengths and resources to overcome any obstacles which may prevent them from attending clinic. In addition, participants in this group will receive all other aspects of the standard of care.

Control Group: Patients will be notified by their hospital clinician 2-3 days prior to discharge that they will be released from the hospital. This gives patients time to notify family members and prepare for their return home. Participants will be provided an appointment to the outpatient HIV clinic of their choosing in Mwanza. The visit will be scheduled within 1 week of discharge. A nurse will meet with the patient for ~30 minutes to review discharge medications and the importance of attending the HIV clinic. Upon discharge, the nurse will escort the patients to the outpatient clinic. The nurse will also take the phone number of patients and call them the night before their scheduled visit to encourage them to go to clinic.

a.vi. Collaborating sites and protection of data: The research will be conducted at hospitals in the city of Mwanza Tanzania (See letter of support from the Director of Bugando Medical Center). Research assistants will collect data on password-protected encrypted tablets into the NIH approved RedCap data management system. Twice daily, the data will be uploaded via the internet onto a secure password protected server at the Clinical and Translational Science Center (CTSC) at Weill Cornell Medicine in New York. We have used the RedCap system for multiple NIH sponsored trials and studies.

b. Source of Materials

b.i. Research material obtained from human subjects: We will be collecting demographic, clinical, social, and behavioral data from participants. **We will not be collecting any clinical samples** (blood, urine, etc.).

b.ii Data that will be collected from human subjects: We will record the participants' name and contact information in a log. The participant will be assigned a study ID number. The identifying data (name and contact information) and the link between these data and the study ID number will be kept in a log in Mwanza and will not be entered into the study data base. The log will be kept in a locked filing cabinet and will only be available to research staff. All other case report forms will be identified only by the study ID number.

b.iii. Access to individually identifiable data: Research assistants will collect data and complete case report

forms on password-protected encrypted tablets into the NIH approved RedCap data management system. Data will be uploaded via the internet onto a secure password protected server at the Clinical and Translational Science Center (CTSC) at Weill Cornell Medicine in New York. The RedCap system is password protected and only senior investigators (Peck, Kapiga), MITU data managers (Myella, Msanga) and statistician/economic analyst (Lee, Murphey) will have access to these data

c. Potential Risks
This study does not include any investigational medications or devices. The risks of this study include loss of confidentiality, social harms, and discomfort answering personal questions. We describe how we will protect against each risk in section 2.

A. Loss of Confidentiality: There is a potential loss of confidentiality of information provided during the study including one's HIV status through participation in the study. Participants randomized to the social worker group will have their HIV status known to the social worker by the nature of the intervention. There is also a risk that the home visit made by the social worker could result in loss of confidentiality. These risks for loss of confidentiality will be documented in informed consent procedures. Participants randomized to the control arm are also at risk for loss of confidentiality if they fail to link to HIV primary care and their HIV disease progresses. We believe that the risk of loss of confidentiality is equal in the two study arms and the same as anyone receiving HIV care in Tanzania.
B. Social Harms: HIV-infected adults are a stigmatized population who are at heightened risk of social harm. Participants may experience social stigma or incur harm because of identification in the intervention or control arm of a HIV-related study. Social harm due to study participation may include loss of privacy, social stigma from perception of being "high risk" of HIV, interference with employment, and discrimination from their family or general public. Of note, adults who participated in our **pilot study cited decreased stigma** associated with receiving support and education from a social worker.
C. Discomfort: Participants will be asked to complete study questionnaires at baseline and at 12 months after enrollment. Questionnaires include topics that may be sensitive such alcohol use, family and social support, and income and education.

2. Adequacy of Protection Against Risks
All MITU clinical research complies with NIH regulations, and with U.S. and Tanzanian laws. Tanzania has a National IRB, which has a US Federal Wide Assurance (FWA) and OHRP Registration FWA00002632. The Weill Cornell Medicine IRB FWA number is FWA00000093.

The Tanzanian National IRB has jurisdiction over all research conducted in Tanzania. All clinical trials conducted in Tanzania must be approved by the Tanzanian National IRB. The Tanzanian National IRB is recognized by and collaborates closely with Regional Medical Officers and hospital directors throughout Tanzania. The Tanzanian National IRB is chaired by Prof. Yunus Mgaya. The IRB has fifteen members who are all independent of MITU and include clinical scientists, biomedical scientists, social scientists, a lawyer, an unaffiliated community representatives and representatives of both Muslim and Christian faith-based organizations. The Tanzanian National IRB requires protocol documents to be submitted at least 10 days in advance of each meeting. Each package contains: 1) a cover letter with the PI's signature certifying that the study will comply with good clinical practices (GCP) requirements; 2) a study protocol; 3) all questionnaires, surveys, informed consents, and education material in both English and Tanzanian Kiswahili; the Tanzanian National IRB meets every third Saturday of the month. A written response is provided within one week. Dr. Peck (PI) has served on a local IRB in Mwanza, Tanzania since 2014 and has practical experience with the nature and application of IRB regulations in Tanzania.

The Weill Cornell Medicine IRB requires documents to be submitted at least 14 days prior to the meeting. Documents that are required for regular applications and expedited applications include: 1) protocol application; 2) informed consent/assent forms in English and Kiswahili; 3) subject recruitment materials and study advertisements, in English and Kiswahili; 4) study specific financial disclosure form for all personnel; 5) Human Research Billing Analysis Form (HRBAF); 6) all data collection sheets, surveys, questionnaires, psychological tests, and interview forms read to or completed by the research volunteer must also be submitted in Kiswahili and English; 7) FDA correspondence; 8) sponsor protocol; 9) investigator's brochure and package inserts; 10) associated grant application; and 11) local language verification statement for all translated documents. Responses to IRB questions or deferrals are reviewed at the following board meeting.

a. Recruitment and Informed Consent

Informed Consent: Eligible adults will provide written informed consent. **Those who do not participate will still be provided with free HIV care and counseling at the hospital and free HIV clinic care.** Research consent forms will be approved by the Tanzanian National IRB and the Weill Cornell IRB. Forms will be translated into Kiswahili and back translated.

The study investigators, particularly Dr. Daniel Fitzgerald (co-investigator), have published extensively on the optimal strategies to assure participants' comprehension of the informed consent form and their voluntary participation in research in resource-limited settings (1–4).

The consent form will include information on study purpose and study procedures, possible risk or discomforts, possible benefits, alternative procedures, confidentiality, right to refuse or withdraw and security of care if they withdrawal. The consent form will also contain information about what participants should do if they have questions about the study; if they wish to withdraw as a participant; if they have concerns about their rights as a study participant; or if they believe they have been harmed by the study including social harms of loss of confidentiality or stigma. The research assistant will emphasize that enrollment is voluntary and that the choice to participate will in no way influence the quality of services they may receive in the hospital or at the HIV clinic. Ample opportunity will be provided to potential participants to ask questions. Consent forms will include contact information for the local investigators.

Once the participant fully understands the study details and expresses a wish to participate, the research assistant will provide a consent form to sign and date in the space provided. The research assistant will also print and sign her name and date the form. The participant will be offered a copy of the consent form to take home. If the participant is illiterate, a thumb-print will be obtained.

Recruitment and informed consent*:* MITU is committed to the ethical conduct of research following the international standards of the Helsinki Declaration and US Federal Registry. MITU has established procedures to assure the **voluntary informed consent** of research participants. Prior to enrolling in a research trial, all potential volunteers are educated about the voluntary nature of participating in a trial; they are also educated regarding delivery of free HIV care in Tanzania, regardless of their participation in a study. Participants are informed of alternatives to enrolling in the study and are informed that declining participation will not impact on their access to care at the facility. Volunteers receive counseling concerning all study procedures, number of visits, risks and benefits of study participation, and alternatives to study participation. Ample time is given to each volunteer to discuss the study and to ask and receive answers to all of their questions and concerns. Each volunteer is given a copy of the signed consent for their records.

b. Protection Against Risks

The following measures will minimize study risks:

A. Loss of Confidentiality: All samples and subject data will be coded at MITU. Each subject will be assigned a study identification number consisting of a unique code unrelated to any patient identifying information, as per Good Clinical Practice guidelines. Any identifiers linked to the participant will be secured and only available to staff at MITU, to ensure subject confidentiality. All source documents will be kept in locked file cabinet. MITU computers and servers are protected by firewall protection and are only accessible with a password. Study staff will be trained in Good Clinical Practice regarding maintaining confidentiality. We will provide intensive counseling and education to all participants on the importance of confidentiality. Participants will be asked to report any breeches in confidentiality and these will be reported to the IRBs and DSMB. During home visits, if asked by friends or neighbors about the purpose of their visits, the social workers will identify themselves as being part of a research study to improve post-hospital outcomes for patients who had been admitted to a study hospital. No mention of HIV will be made. In our formative research, HIV-infected patients informed us that friends, neighbors and relatives had all been aware of their hospital admission and the hospital admission itself was not associated with stigma.
B. Social Harms: Study staff will be sensitized to the challenges experienced by HIV-infected adults as a vulnerable population. They will be trained on how to respond to any social harm reported by a participant. Staff performance will be monitored by the research and intervention coordinators, Dr. Severin Kabakama and Mr. Abel Mary, during quality assurance assessments to ensure minimization

of social harms. Of note, Mr. Abel Mary served as the social worker for the pilot intervention study and has 2 years of experience monitoring for social harm from this intervention. Doctors Peck, Kapiga, Grosskurth will be available to assist the study staff in responding to any event that requires further management. Tanzanian HIV clinics routinely educate all HIV patients clinic on the importance of confidentiality and not sharing information with other patients. Participants will be encouraged to report any adverse event. Study staff will ask each participant about social harms including loss of confidentiality and stigma at each study visit. All adverse events will be detailed in source documents and reported on standardized adverse event forms.

C. Discomfort: As part of the informed consent process, all potential participants will be instructed that they do not have to disclose personal information that they are uncomfortable sharing and that they can withdraw from the study at any time.

3. Potential Benefits of the Proposed Research to Human Subjects and Others

The proposed study has the potential to improve survival of hospitalized HIV-infected patients in Tanzania. People from other African countries may benefit in the future from the knowledge gained in this study.

4. Importance of the Knowledge to be Gained

The results of this study may provide evidence for a new model of HIV care and treatment for HIV-infected adults. Outcomes will be used to better understand factors influencing linkage to primary HIV care and survival. Dr. Kapiga, the Tanzania Site PI of this proposal, is a senior advisor to the Tanzanian Ministry of Health. He will work with the Ministry to create an implementation plan so that our social worker intervention can become a national model of care. An effective social worker intervention can be adapted to similar resource-limited settings. **Nurses** or **community health workers** could fill the role of the social worker in other settings depending upon availability of health care workers.

5. Data and Safety Monitoring Plan

The following monitoring steps will be taken to monitor and ensure the safety of research volunteers:

A. The study and consent forms must be approved by Institutional Review Boards in Tanzania and Weill Cornell Medicine prior to the start of the trial.

B. The Principle Investigator will receive a daily log of adverse events and will review this log each week with the local study team and collaborators.

C. The study team is responsible for reporting all severe adverse events suffered by study participants to the IRBs and DSMB within 24 hours of knowing of the event.

D. The Principle Investigator must renew IRB approval every year through submission of an annual update including a description of all adverse events.

E. A Data Safety Monitoring Board (DSMB) will ensure the safety of trial participants through monitoring study procedures, implementation, study findings and review of all adverse events including social harms. The DSMB is described in full in the next section.

The successful completion of this study has the potential to dramatically improve survival for HIV-infected adults in Tanzania and other resource-poor countries.

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Data Safety and Monitoring Plan

The Data Safety and Monitoring Board will ensure the safety of trial participants through monitoring study procedures, implementation, study findings and review of all adverse events including social harms. It will be chaired by Dr. Serena Koenig (MD), Assistant Professor of Medicine at Harvard Medical School. Dr. Koenig has conducted HIV research for over 10 years in resource-limited settings. She recently completed an NIH-funded clinical trial of same-day HIV testing and ART initiation in Haiti (1).

Bahati Wajanga, MD (Chair of the Department of Internal Medicine at the Bugando Medical Centre) has 10 years of experience as an HIV clinician and researcher in Tanzania. Before become the Chair of Medicine he was employed as physician on the medical wards of Bugando and as a doctor in the Bugando HIV clinic. His research is particularly focused on improving survival for hospitalized HIV-infected adults.

Mr. John Changalucha (Director General of the National Institute of Medical Research in Mwanza, Tanzania) is an internationally recognized public health expert with 30 years of experience conducting HIV research in Tanzania. He has served as site PI for numerous clinical trials performed in Mwanza. Mr. Changalucha is also a member of the Tanzanian National IRB.

The DSMB will meet before enrollment starts to review the study protocol for protection of human participants. The DSMB will then meet every six months via Skype. Prior to their meeting, they will receive summary reports of study progress, all adverse events including loss of confidentiality, stigma, and any other social harm reported by a study participant. Any severe adverse event will be reported to the DSMB Chair, Dr. Serena Koenig, within 24 hours of documentation by study staff. After each meeting, the DSMB will provide a written report on the status of the study and their recommendations for any modifications of the study. This report will be provided to the PI and IRBs. Of note, we have not planned an interim analysis because by the time half the cohort has been enrolled and followed for one year to the primary study endpoint, the other half will have been enrolled, discharged from the hospital, and the 3-month intervention will be complete.

The DSMB has the right to halt the study for safety concerns at any time. The study team, the Weill Cornell and Tanzanian National IRBs, and the DSMB will work closely together to assure the conduct of this study according to NIH regulations for the protection of human subjects and to minimize risks to all study participants.

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INCLUSION OF WOMEN AND MINORITIES:
Women will be included in all study activities. We will recruit Tanzanian adults ≥18 years living in Mwanza. Based upon the characteristics of our patient population in Tanzania, an estimated 50% will be women and greater than 99% of the participants will be black and of African descent.

INCLUSION OF CHILDREN:
No person < 18 years of age will be included in the study.

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