Full Title of trial:

CONTROLLING CHRONIC DISEASES IN AFRICA: DEVELOPMENT AND EVALUATION OF AN INTEGRATED COMMUNITY-BASED MANAGEMENT FOR HIV, DIABETES AND HYPERTENSION IN TANZANIA AND UGANDA

Acronym:
INTE-COMM study

Protocol version number: **1.1**

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Authorised by:

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Signatures			
Dates	11/11/2021		11/11/2021

GENERAL INFORMATION

This document describes procedures for an evaluation of integrated community care for HIV, hypertension and diabetes. It includes the protocol for a cluster randomised trial, comparing an integrated community model of care for HIV-infection diabetes and hypertension with a standard clinic-based care approach in Tanzania and in Uganda. The protocol should not be used as an aide-memoire or guide for the treatment of patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial. Problems relating to this trial should be referred to the relevant Chief Investigator.

Compliance: The trial will be conducted in compliance with MRC Good Practice Guidelines. The trial will adhere to the Liverpool School of Tropical Medicine (LSTM) Governance and Ethics Committee. Approvals will also be sought from the National Health Research Ethics Sub-Committee (NatHREC) in Tanzania and the Uganda Virus Research Institute Research Ethics Committee.

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Abstract

Rates of HIV, diabetes, and hypertension in sub-Saharan Africa have risen sharply and novel models of care will be needed to meet the demand. Our aim is to develop and test a model of integrated community care for the control of HIV, diabetes, and hypertension. The key questions that we are asking are:

- Is integrated community care approximately as effective as standard facility-based integrated care in terms of blood pressure and fasting glycaemia control among people living with hypertension or/and diabetes.
- Can integrated community care improve plasma HIV viral load suppression among people living with HIV. These people may or may not have diabetes or hypertension?
- What is the uptake and retention in care with community care? What is its acceptability?
- What are the costs associated with community care (for patients and health services) and what is its potential cost-effectiveness?

We will conduct a pragmatic cluster-randomised trial comparing a community integrated care strategy with standard clinic-based integrated care in Tanzania and Uganda. Patients with HIV, diabetes or hypertension who are considered stable on treatment at the health facilities will be invited to join the research. They will be organized into groups of 12 persons based on their residence in a ratio of approximately 2 persons with diabetes or hypertension to 1 person with HIV. The groups will then be randomised to either integrated community or integrated facility care.

Those randomised to the community arm will have their care devolved to the community – usually a low level health point. They will receive their drugs, adherence support and monitoring in their groups at this community point. Groups randomised to facility care (control group) will continue to receive integrated clinic-based care. All study participants will be followed up for 12 months. The study has two co-primary endpoints: a composite endpoint of glycaemia and blood pressure control among individuals with diabetes and/or hypertension and plasma viral load suppression among individuals living with HIV.

For the power calculations, we have taken clustering into account and assumed that the intra-class coefficient will be rho=0.02. Our target sample size available for analyses is 116 groups, each comprising 12 persons (8 with diabetes or hypertension and 4 with HIV). This will provide over 80% power to detect an absolute difference in risk of diabetes and hypertension control of 10% (i.e. 50% versus 60% achieving good control in the 2 arms would be statistically significant at the 5% two-sided significance level). Power will be very high for differences larger than this. For the HIV viral suppression endpoint, we assume that viral suppression is close to 90% and that the primary aim is to show non-inferiority with the community-care arm (and secondary analyses will compare superiority). The trial will have over 80% power to show non-inferiority with a margin of delta= 8.5%, 7.5%, and 5.5% assuming viral suppression is 85%, 90% and 95% respectively. To allow for losses to follow-up, our target for enrolment is 124 groups each comprising 14 participants (i.e. a total of 1,736 participants).

Data will be analysed using Generalised Estimating Equations with the primary analysis comparing proportions of patients achieving viral suppression, blood pressure and glycaemic control. We will calculate costs of health care delivery and costs patients incur to access health care (i.e., societal costs) and link these data to estimates of effectiveness to estimate potential cost effectiveness.

Background

Our aim is to conduct research that informs governments in sub-Saharan Africa (hereon referred to as Africa) on health care delivery strategies to reduce the mortality and morbidity from chronic conditions (principally HIV, diabetes and hypertension). These are all common conditions that require life-long care. They mostly affect adults of working age. They require common approaches in terms of monitoring and adherence and lifestyle support and systems for regular follow-up and treatment of patients. All three conditions are manageable with existing medicines and diagnostics that are available readily.

Mortality from HIV in Africa has fallen from a peak of just over 2 million deaths a year in the early 2000s to just under half a million a year, thanks to the scale-up of antiretroviral therapy. In contrast, premature adult deaths from diabetes and hypertension are now estimated to be around 2 million a year and rising.

One reason for the high death rate from diabetes and hypertension in Africa is that few people with these conditions – probably only 5-10% - are in regular care (Atun et al., 2017), and among these few, the control of blood pressure and glycaemia is poor, as our research and that of others has shown. Thus, models of care are needed that both retain patients in care and improve their health outcomes while being cost-effective for health services.

Why evaluate integrated management of chronic conditions: At present health care provision for chronic conditions is fragmented, which leads to inefficiencies and a waste of resources. For example, clinics for diabetes and hypertension care are often run separately from each other and diabetes in some settings is managed only in higher facilities. The clinics are generally poorly resourced. In contrast, HIV care is well-resourced and HIV is managed separately from other conditions, in separate dedicated clinics with dedicated physicians, separate triage, waiting areas and pharmacy, and has a separate funding stream. This vertical nature means, for example, that there is no learning gained by HIV control to controlling the rapid rise in diabetes and hypertension. Patients who have multiple conditions have to attend multiple clinics, which incurs catastrophic transport costs for patients as availability of transport is limited. Health facilities have to run multiple clinics and pharmacies, which results in duplication.

Although vertical programmes are probably inefficient and costly, within the fragile health systems in Africa, vertical HIV programming has provided high quality care for people with HIV such that almost 80% of people with HIV are in regular care and about 90% of these virally suppressed. Changes to the HIV model of care could disrupt patient follow-up and worsen patient retention and clinical outcomes. Therefore rigorous research to determine the potential benefits and harms is needed.

In response to this need, and with funding from NIHR and the EU, our Group has been evaluating the bringing together of vertically delivered HIV services (generally well-resourced and protected) and diabetes and hypertension care (currently less structured and poorly resourced) in Tanzania and Uganda under one roof. This approach was innovative, unique and risky. However, with support from and in partnership with policy makers and disease control programme managers, we have successfully established and have been evaluating this "integrated care clinic" model.

Why evaluate community care? The challenge now is that the prevalences of chronic conditions among adults are already very high. In most African settings, about 5% of people are living with HIV, 4-7% have diabetes, and around 25% have hypertension. On top of this, health facilities across the whole of Africa have a severe shortage of clinically qualified staff. However, control of blood pressure and glycaemia is poor even in research settings where patients have good access to medicines and clinical monitoring. Thus, clinic-based care alone will not meet patient demand for people with diabetes or hypertension even if we identify efficient ways of organising care; and patient outcomes may continue to be poor even if the quality of care is improved (e.g. as found in research studies).

Because of these reasons, our Group was urged by health services in Tanzania and Uganda to evaluate decentralising integrated care to the community-level and that is the basis of this protocol. Our primary research question for the proposed research is: **what is the effectiveness of community-based integrated management of HIV, diabetes and hypertension in comparison to clinic-based integrated management of these conditions in terms of patient outcomes?**

To address this question, we will adapt the community-based models of HIV care that include provision of medicines, peer-support, and self-management for integrated community care for HIV, diabetes, and hypertension. This integrated community care model has been built in consultation with different stakeholders including patients and policymakers. This proposal outlines how it will now be evaluated against standard clinic-based care in a randomised study to generate evidence that policymakers can use to consider whether and how the model could be scaled up.

Study setting

Our research on integrated clinic-based care for HIV, diabetes and hypertension is being conducted in Uganda and Tanzania. The two countries were chosen because their public health services are strongly committed to providing services for non-communicable diseases, but they are struggling to scale-up provision for diabetes and hypertension in the face of competing health demands, including from HIV. In these countries, the research team has a good understanding of the local setting and strong links with researchers, health care providers, and policy makers. The proposed research on integrated community care will be based in the same settings as the research on clinic-based integrated care. Table 1 shows the basic characteristics of these countries.

Table 1: Profile of Uganda and Tanzania regarding the prevalence of the three chronic conditions (hypertension, diabetes, and HIV) and doctor density

	Tanzania	Uganda
Income level	Middle	Low
Population size	62m	48m
Estimated prevalence of hypertension from STEPS survey	26%	26%
Estimated prevalence of diabetes from STEPS survey (Manne-Goehler et al., 2016) *	5-10%	2-5%
Estimated prevalence of HIV-infection	5.1% (2017)	6.2% (2017)
Doctors' density /100,000 population	3 (2014)	0.8 (2005)

** Diabetes estimate varies according to age and gender. Data are of variable quality but Manne-Goehler et al. (2016) shows that the overall median diabetes prevalence in 12 countries in Africa is 5%*

Both Uganda and Tanzania have strategic plans, operational manuals, and clinical guidelines focused on the delivery of HIV. The strategic plans affirm differentiated service delivery models for Antiretroviral Therapy (ART) integrated with NCD care as crucial (see *Annexe 1: Scoping review summary report*). The two countries have existing national guidelines for the management of hypertension and diabetes. Drugs for all three conditions are available for free in Uganda, although shortages are common. In Tanzania, HIV medicines are free. Medicines for hypertension and diabetes are sometimes provided for free by government health facilities that prioritise such purchasing. However, usually these medications have to be purchased by the patient or they are provided through private medical insurance schemes, to which about 50% of the population in Dar es Salaam (the capital of Tanzania) will belong. Two types of schemes are common: the national insurance scheme which covers all government employed workers (and is compulsory) and the community scheme which is popular among poorer communities. In addition, the private sector also covers its employees. The costs of medication, when purchased by facilities from government medical stores, is low.

We have been discussing patient access to drugs with the public health services in Tanzania and Uganda for five years. Our estimation is that although access is currently erratic at times, access should improve in the next few years, as disease control programme managers have been preparing for more investment in the prevention and management of non-communicable conditions including diabetes and hypertension.

During our research programme, health facility managers and district and national policy makers have agreed to work together to ensure timely ordering of sufficient drugs supply and to re-prioritise clinic-level funding to ensure drugs availability. Further, the research programme will provide buffer supplies of drugs, which can be accessed by clinics when needed.

Challenges of integrating diabetes, hypertension & HIV at a community level

We have accumulated knowledge on different types of community care being used to manage chronic conditions. Much of this knowledge is from HIV. The HIV community care model has been implemented in settings in Uganda and Mozambique but scale up beyond these countries has been limited, despite first being employed over 10 years ago, in part because of limited rigorous evidence of effectiveness.

We cannot simply apply the models of community care for HIV to community integrated models of HIV, diabetes and hypertension care. There are important differences between diabetes/ hypertension management and HIV management, which must inform on how these conditions could be managed in the community. These are detailed in Table 2. Most patients can respond to and tolerate standard first-line antiretroviral regimens whereas stabilising patients with diabetes and hypertension, even if a reliable supply of medicines is available, can be more complex.

Table 2: Differences in the challenges of controlling diabetes and hypertension

Criteria	HIV	DIABETES OR HYPERTENSION OR BOTH
Diagnostic delay	These days, majority of patients start antiretroviral therapy > CD4 count 250 /μl (i.e. when they are relatively healthy).	Hypertension is usually a silent disease. Diabetes causes complications but usually after 10y. Often both conditions are detected when the person becomes sick with complications (e.g., CVD event).
Treatment initiation	Therapy is started immediately in anyone who tests positive with HIV.	It takes time to diagnose, and the first intervention should be diet and lifestyle if diagnosed early
Treatment tolerance	Vast majority tolerate standard first line antiretroviral regiments.	For both conditions, therapy needs to be tailored (i.e., adjusted over many months)
Treatment side effects	Side-effects are usually minor and decline rapidly within 2-3 weeks.	Side effects can appear within hours, days or months later (e.g., persistent dry cough with ACE inhibitors which can develop many months later)
Disease control	Exceptionally high adherence is needed to maintain suppression of the virus.	Not an infectious disease
Treatment substitutions / changes	Patients adherent to antiretroviral therapy can remain on the same combination for decades.	Even if patient is perfectly compliant, he/she will likely need treatment adjustments over coming years, particularly with diabetes as this is a progressive disease.
Patient outcomes	Very little influences the survival of the patient except for antiretroviral therapy.	Diet and lifestyle behaviour modification is crucial in addition to (and sometimes instead of) drugs.

Measures of control	HIV viral load declines rapidly within the first few weeks and by 4-5 months, the vast majority will have undetectable viral load.	Blood pressure and glycaemia decline rapidly with the right treatment. However, there is no criteria for achieving stability.
Routine monitoring	From about 6 months, patients should be monitored for viral load, ideally every 3-6 months although many practices in Africa do this annually or when failure is suspected clinically.	Patients with diabetes and hypertension usually need a similar level of monitoring though knowledge on markers is not as good.
Patient empowerment	People living with HIV are generally knowledgeable about the infection, the medicines, and the potential side-effects.	People with diabetes and hypertension may be much less empowered. Quality of management by health care workers might also be variable.
Stigma	HIV is a stigmatising disease which affects patients' access to care. HIV care in health facilities is organised separately from other services.	Much less stigma with diabetes and hypertension. In many clinics, health care for these conditions is available alongside other conditions.

Differences in the current management and control strategies for HIV care and for diabetes or hypertension.

HIV medicines are now typically dispensed at 3-monthly intervals from medium-large sized primary health care facilities that have a part-qualified medical officer or physician. Diabetes is still sometimes managed from higher-level health facilities (large health centres and district hospitals) and hypertension from most primary care facilities.

In HIV, the emphasis is to get the patient to take the medicines consistently and achieve a high-level of adherence. Thus, patients receive treatment adherence counselling each time they visit for whatever reason. Routine clinical examinations or laboratory monitoring reveal little. Among patients failing on treatment, rising levels of viraemia can be detected weeks to months before the patient becomes sick if they are tested routinely for plasma viral load.

With diabetes and hypertension control, there is limited availability of medicines as discussed above. We think that this is one reason why patients with these conditions are usually seen at clinics monthly or more frequently (even after they are stable on treatment) as health facilities do not have the medicines to give to patients for a longer duration. Patients are tested at these times for glycaemia or high blood pressure when they attend clinic and may have other examinations. Thus, diabetes and hypertension models of care are more medicalised than models of care for HIV.

It is unclear how often routine monitoring should be done among patients with diabetes or hypertension who are stable on treatment. Regular monitoring is costly (e.g., in terms of the time it takes health care workers to do it). Could it bring benefit over and above adherence

counselling if done frequently? For HIV, monitoring of viral load (and other clinical and laboratory markers) used to be done regularly, with viral load recommended at least 3-monthly, but today in Africa few patients have laboratory markers and viral load is tested annually in some settings. In others, it is done only when clinically indicated.

Clinic-based integrated care compared with standard vertical care for HIV, diabetes and hypertension

We have created a clinic that can provide integrated care services for HIV, diabetes and hypertension and have tested this in small numbers of patients in selected health facilities. The development of this model was done and first tested in an initial study, called the MOCCA study. We then started a large phase III trial to compare integrated versus standard vertical care (called the INTE-AFRICA trial). These studies showed that integrated management is acceptable to patients (e.g. there was high uptake to join the research) and that it is potentially cost effective (e.g. the cost of treating a person with two or three conditions was only marginally higher (between zero and 15% more than treating a person with single disease) (Shiri et al BMC Medicine 2021). The details of these studies are below. More recently, health services in Uganda have started to scale-up integrated clinic-based care in a few facilities. These are described further below.

The MOCCA study: Between August 2018 and May 2019, our group conducted the MOCCA pilot study (Management of Chronic Conditions in Africa). We provided integrated care at 10 health facilities that were offering primary health care services, five of which were in the Dar es Salaam, Tanzania, and the other five, in and around Kampala, Uganda. The results of this study have been submitted for publication. The findings from the costings study showed that integrated clinic-based management has the potential to be highly cost-effective (Shiri et al, BMC Medicine, in press).

Briefly, most patients approached agreed to join the MOCCA study whether they had a single chronic condition or had multiple conditions. Overall, 2,273 patients were enrolled and followed up for a median of just over 8 months. The proportions alive and retained in care at study end were high among all participants: 83% among people living with HIV, 85% among those with diabetes, 79% among those with hypertension and 91% among those with multiple conditions.

Although the retention rates were high, and there were improvements in blood pressure and diabetes markers at study end compared with baseline, the control of blood pressure and of blood glucose were suboptimal. Among all persons who had hypertension (whether alone or in addition to diabetes or HIV), just 54% had good control of blood pressure (defined as blood pressure <140/90 mmHg). For diabetes, just 24% had good control of their fasting blood glucose (<6.1 mmol/L). Control of these conditions, particularly high blood pressure, is a global challenge even where low-cost medicines are available (e.g. see Mills et al Circulation 2016; 134: 441-450 and Mills et al Ann Intern Med 2018; 168: 110-120).

In contrast, patients living with HIV did retain good control of virus levels in the integrated clinic, with virus well suppressed in 89% of the participants (<100 copies per ml).

Analyses of costs showed that integration of services reduced both health service costs and household costs and could be an efficient way of increasing coverage of services for diabetes and hypertension (Shiri et al, BMC Medicine, https://doi.org/10.1186/s12916-021-02094-2).

THE INTE-AFRICA (Integrating and decentralising HIV, diabetes, and hypertension services in Africa) study: This is a follow-on from the MOCCA study. It is a pragmatic parallel arm cluster-randomised trial comparing integrated health services for HIV, diabetes and hypertension compared with a standard care approach (i.e., vertical stand-alone care) in Tanzania and in Uganda. The trial is being conducted in 32 health facilities: 16 assigned to integrated care and 16 to the control arm comprising standard vertical care for each of these three conditions. A total of 7,047 patients have been enrolled into the trial and are being followed up for one year. Follow-up will end in April 2022. We plan to disseminate the knowledge (the research evidence and process measurements) learned from this study both nationally and globally to inform effective control of diabetes and hypertension (alongside HIV control) in low-resource settings.

The scale-up done by the health facility managers in Uganda: One weakness of the MOCCA and INTE-AFRICA studies is that in both studies, only small subsets of patients attending the health facilities were enrolled into the integrated care clinics, and the evaluation was based on these samples, while vertical clinics continued to operate in parallel at those health facilities. The MOCCA study was completed in 2020 and the research team stopped working in the 10 health facilities, of which 5 were in Uganda (4 government and 1 non-governmental organisation). They were expected to return to offering study patients vertical care while we await the results of the large INTE-AFRICA study. However, shortly after the research team left the MOCCA health facilities in Uganda, the 4 government clinics in which the MOCCA study was done, implemented integrated management for all patients with either HIV, diabetes, or hypertension. The clinic managers did this independently, without discussion with each other or with the research team. They made these decisions based on observations that they made during the research. To ensure uninterrupted drug supply for diabetes and hypertension, the health facilities have facilitated patients to set up “medicines clubs” for patients with diabetes and hypertension. Under this arrangement, patients contribute a small amount of money each month into a central joint bank account and the club bulk buys medicines at substantially reduced prices (bulk buying reduces a patient’s monthly costs to less than £10 per patient, less than half of the cost of direct purchase from a pharmacy). These clubs took 2-3 months of meetings and planning to set up.

Initial concerns to scaling up integrated management in these four clinics came from clinicians fearing that people with diabetes and hypertension might be deterred from attending an integrated care clinic and people with HIV might fear the effects of integration on their outcomes. There seemed to be no reservations about integration from patients and now some months later, integrated management remains popular with patients and with the health care providers.

The health facility managers note (anecdotally) that there has been a reduction in stigma for people with HIV and people with diabetes and/or hypertension have not observed stigma. They also believe that integrated management seems to reduce duplication and reduce costs for health facilities more than was estimated in the MOCCA study when this is scaled up in real-life. Discussions of these engagement exercises are summarised on our website (www.lstmed.ac.uk/RespondAfrica).

Scope of the INTE-COMM study

Because we want to achieve a global impact, we will be conducting the INTE-COMM study in two countries. We also believe it is essential that the evaluation uses rigorous research methods and involves a randomised trial to generate evidence that can be used by policymakers. This is important for the future scale-up and sustainability of this model of care. As mentioned above, community care models for HIV, deployed in some settings in Uganda and Mozambique, have not had widescale uptake and we believe that this is because they were never evaluated rigorously in comparative studies. Community care involves a major change to the way in which health care is organised. For example, it could involve medicines to be dispensed by non-pharmacist, non-clinical staff in a non-clinical setting. To influence change in such settings probably requires trials evidence. We will do the research with the involvement of both governments, patients themselves and the Non-Governmental Organisation (not-for-profit) led health services (i.e., in a range of health facilities). Our aim is to develop and test a model of community-based integrated care and management of HIV, diabetes, and hypertension for scaling up in sub-Saharan Africa.

Our primary study, a cluster-randomised trial, will measure effects on clinical outcomes and determine cost-effectiveness. This is important for policy considerations.

Study objectives

1. To develop a new model of community-based integrated management of HIV, diabetes, and hypertension.

2. To determine the effectiveness of community-based integrated management of HIV, diabetes, and hypertension in comparison to clinic-based integrated management of these conditions in terms of patient outcomes, acceptability, and potential cost-effectiveness.

Conceptual framework

Community models for chronic conditions in Africa are rare (Egbujie et al., 2018; Fisher et al., 2017). A number of initiatives have been developed for the management of HIV-infection that involve peer support and self-management (Decroo et al., 2017), and these are increasingly being used in both Tanzania and Uganda. Our model differs from existing community care approaches. It will include provision of drugs at the community level and involve management of multiple chronic conditions.

As mentioned above we have used the learning acquired from organising HIV vertical community care models to design integrated community care for HIV, diabetes, and hypertension. Our starting point was that community care should comprise group-based care involving peer-support and self-management. This includes an emphasis on adherence to drugs and on advice on diet and lifestyle modification. In a large trial in Uganda with over 3-year follow-up, we showed that a focussed approach that plays to the skills of lay-workers (in building rapport with clients and promoting adherence) was as effective as clinic-based doctor-led care in the management of HIV-infection (Jaffar et al., 2009).

The INTE-COMM study will involve a complex intervention (O'Cathain et al., 2019), involving multiple components (drug delivery system, adherence support strategies, peer support, self-management, facility-linkage, and health education), and will require changes in the behaviour of patients and healthcare providers. The conceptual framework for the INTE-COMM study is illustrated in *Figure 1*. We have followed the updated MRC framework for developing and evaluating complex interventions and frameworks for intervention adaptation, multi-morbidity intervention and rigorous evaluation (Craig et al., 2008).

Narrative for the INTE-COMM conceptual framework: The revised MRC framework identifies key elements of the intervention development and evaluation: development, feasibility and piloting, evaluation, and implementation. The model advocates for a phased approach to the development of the model involving the use of best available evidence, appropriate theory, and a series of pilot studies, prior to definitive evaluation and eventual implementation. A process evaluation is conducted alongside the intervention to assess fidelity, clarify causal mechanisms, and identify contextual factors associated with variation in outcomes.

Our activities to develop the community care model have comprised:

- A scoping review of empirical and grey literature including government policy documents of community care.

- Discussions with researchers doing similar research that is not yet in the public domain (for example researchers who are part of Global Alliance on Chronic Diseases).

- Discussions with patients, community leaders, health care providers, policy makers/senior management and relevant international organisations/non-governmental organisations to better understand their views on the acceptability of different approaches to community care. We have also used our national steering committees, which have representation from all the stakeholders including high-level policy makers.

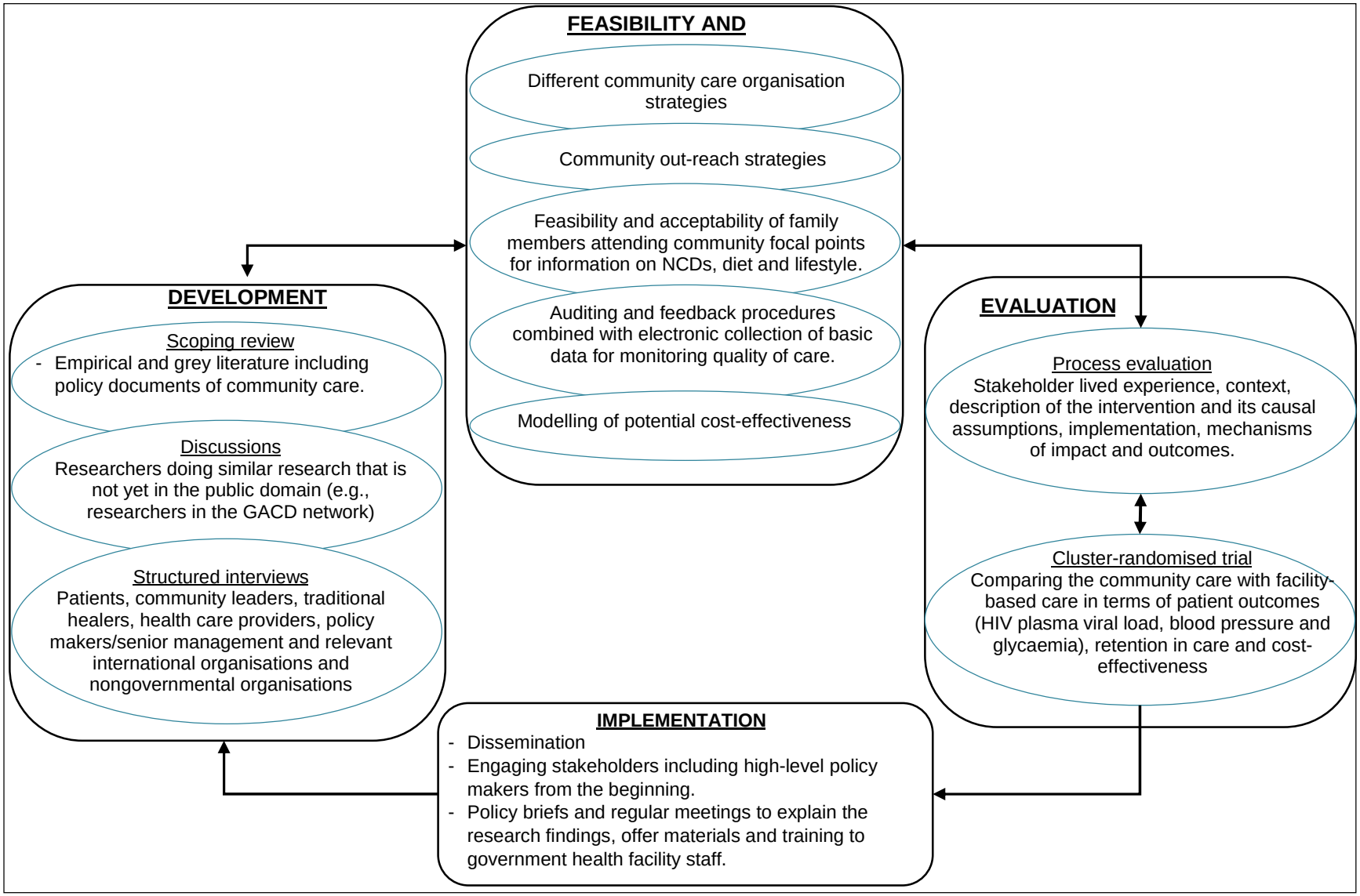


Figure 1 Conceptual framework for the INTE-COMM study

Methods

Development of the integrated community care model

i. Scoping review

The scoping review was conducted based on the framework developed by Arksey & O'Malley (Arksey & O'Malley, 2005) and refined by Levac et al (2010) which was further validated through broad inter-professional team experience (Daudt, van Mossel, & Scott, 2013). The framework consisted of five steps, which included: a) identifying the research question; b) identifying relevant studies; c) selecting the studies; d) charting the data; and e) collating, summarizing, and reporting results. A consultation exercise was undertaken with key stakeholders to complement and add value to the literature search.

The scoping review is attached as an appendix. In brief, we categorised community-based interventions into six general design groups, including those that involved i) improving access to medications (specifically ART), ii) providing treatment support programmes, iii) multifaceted support programmes, which comprised several interlinking interventions iv) home visits from community health workers, v) support via SMS text messages and vi) differentiated care. Where research had compared patient outcomes between community and alternative care (i.e., usual care), the majority found that outcomes were either improved, or at least no worse than the standard care, though study design and quality of implementation varied across different studies. This body of research seems to suggest that a suite of interventions may be more effective than a single measure.

From a range of government policies from Tanzania & Uganda, four community-based interventions are recommended for the treatment of patients with HIV and are accompanied by clear and detailed methods for their implementation in practice. These involve improving patient access to antiretroviral therapy (and so crosses over with the research category above). Though the importance of integrating HIV care with other conditions (including non-communicable conditions) is highlighted as important for future care provision in several health strategy documents, no specific community-based interventions are detailed.

Of the ongoing Global Alliance for Chronic Diseases projects without publications, all focused on the use of mHealth methods, either used or supporting community health workers to improve multiple aspects of hypertension or diabetes care based in the community. This appears to be a developing area relating to chronic diseases care.

Thus, there is currently no clear evidence for a community-based model of integrated care for HIV & non-communicable conditions. However, there is policy and research evidence for several different models of effective community-based care for HIV, and research findings (though limited) supporting hypertension or diabetes care in the community.

ii. Discussions with policy makers, patients, health facility managers

We held several engagement exercises with policymakers, patient and community leaders and facility managers over the last 2-3 years. The most recent consultations were done 3-7th May in Uganda and 7-8th June in Tanzania.

The questions that we have asked patients, health facility managers, and policymakers were:

1. Where should patients get their treatments from when they are considered clinically stable? What challenges do you foresee with the different approaches?
2. How often should this happen within the community? Where in the community should it happen?
3. How should Groups be formed? Who are stable patients? Who should contact / consent patients?
4. How often should BP and glycaemia be tested?
5. How often should the patient visit the health facility **routinely** to see a doctor?
6. What is an ideal size of the Group and how long (in duration) should they meet for?
7. Will stigma (associated with HIV) be a challenge in the community?
8. To policymakers we asked what sort of model would be attractive to them and what type of data would they need for their policy considerations.

Questions we did not ask are around who should pay for the drugs (discussed below). We also did not ask whether group care should be integrated or vertical since from previous discussions with senior health care managers and policymakers, it is very clear that *integrated* community care was the preferred strategy.

Supply of medicines

We have discussed the challenges in an article (Shayo et al., 2020) and briefly above. Shortages in medicines supplies for diabetes and hypertension are likely to be common. In Tanzania, many patients will have insurance or the means to pay. Those who cannot pay are usually supplied free medicines by the health facilities. In Uganda, some clinics where we have been working have mobilised patients with diabetes or hypertension to form 'medicines clubs' whereby patients put money into a central pot, which is then used to purchase medicines at low-cost. The contribution per patient then works out at about £5-£10 per month.

Medicines supply for diabetes and hypertension in both countries is improving with time but it is likely to be challenging during the course of this study. We will not interfere with the efforts of health services and patient groups but document the regularity of supply of medicines for study participants. In addition, we will provide buffer supplies for health services for use with study participants, as we have done in previous studies, to ensure that they have adequate supplies.

This support will be designed to ensure that patients have access to basic medicines for diabetes and hypertension management. This is essential since without medicines supply, patients tend not to attend health services (and so cannot be part of research studies). The support that the research team will provide will be minimal to ensure the conditions remain close to normal health service conditions. The findings will be generalisable to settings which have a reasonably reliable supply of medicines, which is likely to be most settings in Africa soon.

Theory of change

The INTE-COMM Theory of Change (Figure 2) is a pragmatic framework that illustrates how and why we believe the INTE-COMM model of integrated community care will be effective. The overall goal of the project is to design and evaluate a community model of integrated chronic care that is effective at ensuring positive patient outcomes, is affordable to the healthcare system and is acceptable to both the patients and the community. The Theory of Change shows what change is necessary as a precondition to move up the causal pathway.

Based on experience with integrated clinic-based care in both the MCOCA study and INTE-AFRICA trial and our informal discussions with patients participating in the two studies, we believe that stable patients will embrace community care as it will reduce out-of-pocket expenses related to transport fares and will help them save time due to reduced waiting times. This way, we will be able to keep more patients in care. We also think that if we explain to the nurses and clinicians that down-referral of stable patients to the community will ensure that the meagre health facility resources will be reserved for the fewer unstable patients, they will be more likely to support the INTE-COMM intervention.

Based on our experience with differentiated models of care in HIV and the performance of lay workers in supporting community-based health programs in the region and elsewhere, we believe that Community Healthcare Workers and Village Health Teams will be able to deliver drugs to patients in the community, provide adherence support, and support self-monitoring, with the appropriate training and support supervision.

The Theory of Change will be tested in the initial feasibility and piloting of the project. We will evaluate the assumptions articulated in the Theory of Change to formulate research questions during this phase. This will enable us to identify and strengthen weak links in the causal pathway. We will revise the intervention where necessary. During the intervention, the Theory of Change will form the basis of the study's process evaluation. We will keep track of input, process, output, and outcome indicators based on the assumptions of the Theory of Change with a clear focus on measuring whether key stages in the causal pathway are achieved.

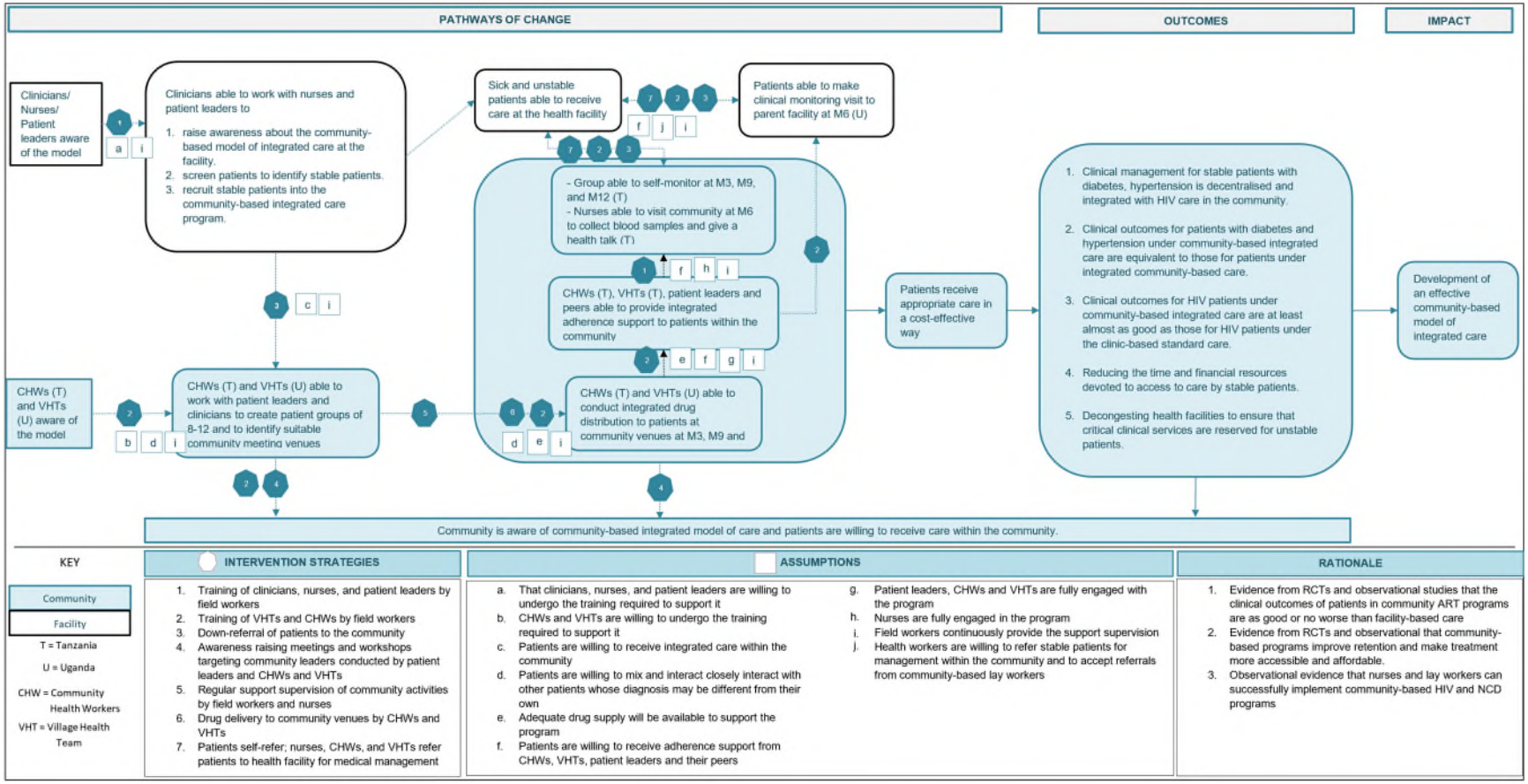


Figure 2 INTE-COMM Theory of Change

Study design

Primary endpoints

The trial will have 2 co-primary endpoints:

i) **Plasma viral load** suppression for patients living with HIV-infection.

ii) A composite of **glycaemia and blood pressure control** for those living with diabetes and hypertension respectively.

Secondary endpoints

These will include retention in care, costs, and potential cost-effectiveness.

Based on the discussions above, we plan a pragmatic cluster-randomised trial. A community care strategy will be compared with standard clinic-based care. Both will provide integrated management for HIV, diabetes and hypertension. The trial arms comprise the following arms (Table 3):

Table 3 Description of the two study arms for the proposed cluster-randomised trial

Activity	**Integrated community care arm**	**Standard integrated facility-based care**
Led by	A nurse and a trained lay-worker (known as village health worker in Uganda, community health worker in Tanzania).	Standard facility-based care led by a clinician
Group size and meeting location	8-12 patients. The first meeting will be at the health facility. The rest will be in low-level facilities / community points. The trained lay-worker and nurse will visit the Groups at those location.	Patients will be placed into artificial groups of 8-12 patients to enable comparison. They will continue to receive their care from the facility.
Frequency of meetings / group appointments	Monthly meetings in the community organised by the trained lay-worker and the nurse.	Standard monthly visits as is common at present across East Africa.
Frequency and location of routine monitoring (when no complications / problems suspected)	Blood pressure and glycaemia will be measured by the nurse in the community when she accompanies the trained lay-worker. This monitoring will be done roughly at the same frequency as in the facility.	Normal monitoring will occur, done by clinic staff. This will typically involve monthly monitoring of blood pressure and 3-monthly monitoring of glycaemia.
Who collects the drugs from the health facility pharmacy and frequency of dispensing?	Drugs will be dispensed at the health facility into medicine bags and taken to the community by the nurse and distributed to patients	Standard collection from the health facility pharmacy
Adherence / behavioural information and support	Done by the trained lay-worker, the peers and patient leaders in the community and overseen by the nurse	Standard as provided by the health facility to all patients.

Low-level facilities will generally be health centre level 2 in Uganda and health posts in Tanzania. For a small number, a central location (e.g. a church or town hall) will be used.

The village health care worker is also known as the community health worker in some settings. These individuals will be hired for the project where we cannot find existing government village health workers to take on this role because already have high workloads and are unable to take on further tasks. The village health workers hired will be similar in qualifications to existing government village health workers and they will be provided with basic training in HIV, diabetes and hypertension. Ministry of Health guidelines will be followed in the selection of these lay-workers. They will all be paid by the project to ensure that they are dedicated to the project. The pay rate will be to those paid by government.

Patients who are not stable clinically (who will require more frequent monitoring will not be enrolled – see below). Participants who are enrolled but subsequently require more frequent monitoring on clinical grounds will usually be referred up.

We chose the groups to be organised by both a nurse and a lay-worker. The trial is designed to test superiority of community care. This is important as standard clinic based care, even when the quality of care is good, continues to have poor outcomes for patients (e.g. less than 50% of participants achieved adequate control of hypertension and diabetes in our earlier MOCCA study – Birungi et al 2021; Shiri et al 2021). Both the nurse and lay-worker will provide a more comprehensive level of care. Patients will likely be processed much quicker and so will have less waiting. Having a nurse handling and dispensing medicines will ensure that the findings will be more relevant across sub-Saharan Africa, including in countries where regulatory frameworks do not allow non-clinical workers to be involved in the dispensing of medicines.

We considered the groups being organised by patients rather than a village health worker and a nurse. In this model, groups of patients would meet at a convenient location and patient representatives would take turns to visit the health facility to pick up medicines for the all patients in the group. This model has been employed in HIV control in Uganda and Mozambique. However, as discussed above, we felt that this would run into regulatory problems in the real world as few countries in Africa would allow drugs for one patient to be collected by another.

We considered a community model involving small private pharmacies, known as ADDOs in Tanzania. They are many in number, but some do not have space for groups to meet. However, this could be an important model of care for people with diabetes and hypertension in Tanzania. Therefore, during the research trial, we will map out these outlets and assess the feasibility of using them in future. This will include assessing space for meetings and speaking with ADDO owners.

Stigma: One potential challenge with community care is that it could lead to disclosure of the disease/condition that the patient has. In Tanzania, some patients with diabetes and hypertension have suggested that we consider the community model restricted to people with

these conditions and exclude those with HIV as they are reluctant to be associated with them.

However, in the MOCCA and INTE-AFRICA studies, which involve integration at the health facility, integration appeared to be acceptable given that few declined to join the research and few withdrew. Public health services are also moving towards integration, as mentioned above. Therefore, in the community care model, we will maintain integration. Adherence counselling will be general, covering all 3 conditions and where patients request, their medicine bags/pill boxes will be concealed so that other patients cannot determine the conditions for which the patient has received medication.

Village Health Teams

As mentioned above, the staff we plan to hire will have similar qualifications and similar pay and conditions as government village health workers. They will receive training in the following areas:

- Diabetes, hypertension and non-communicable disease control, including their risk factors, monitoring including signs of progression to disease.
- Diet and lifestyle behaviour for diabetes and hypertension
- Infection prevention and management
- Adherence support/counselling
- When to refer and not refer patients in the community to the health facility.

Meetings and venues

These will be health posts in Tanzania and level 2 health centres in Uganda or they will be places of worship. They will be chosen to be within walking distance or a short bicycle or taxi ride away (and generally much more accessible than the health facility).

The first Group meeting will be at the health facility, organised by a nurse, and subsequent meetings will be in the community, organised by the village health worker, supported by the nurse. For this first meeting, patients will receive compensation for transport as at this visit we will be asking them to come in and taking informed consent from those who agree to participate.

Randomisation/Selection of participants

We will work in about 10-16 health facilities across Tanzania and Uganda, which are largely urban and peri urban sites. In Tanzania, these facilaties are part of the MOCCA and INTE-AFRICA studies and now operate integrated care for diabetes, hypertension, and HIV. In Uganda, we will just recruit from INTE-AFRICA sites. MOCCA and INTE-AFRICA studies comprised 42 health facilities between them and so we do have ample ability to increase the number of facilities if recruitment is slower than anticipated. These facilities are all doctor-led. In Uganda, they are the larger health centres. In Tanzania, they are mostly hospitals.

The health facilities will be selected from the following:

- *Uganda*:
  Kasangati HC IV, Kinoni HC IV, Kyazanga IV, Mpigi HC IV, Muduuma III, Namayumba HC IV, Namulonge HCIII, Ruhoko HC IV, Sekiwunga HC III.

- *Tanzania*:
  Amana, Mwanyamala, Temeke, Mbagala, Hindu Mandal, Sinza, Mnazi Moja, Cardinal Rugambwa, Bagamoyo, Kisarawe

At each facility, patients who fulfil the criteria will be formed into groups of 8-12 people based on their location and their disease/condition. The groups will be randomised to the study arms (Figure 3). Randomisation will be computer generated. It will be stratified by health facility, based on their infrastructure: hospitals and health centres with in-patient facilities, primary care health centres offering out-patient facilities and not-for-profit facilities.

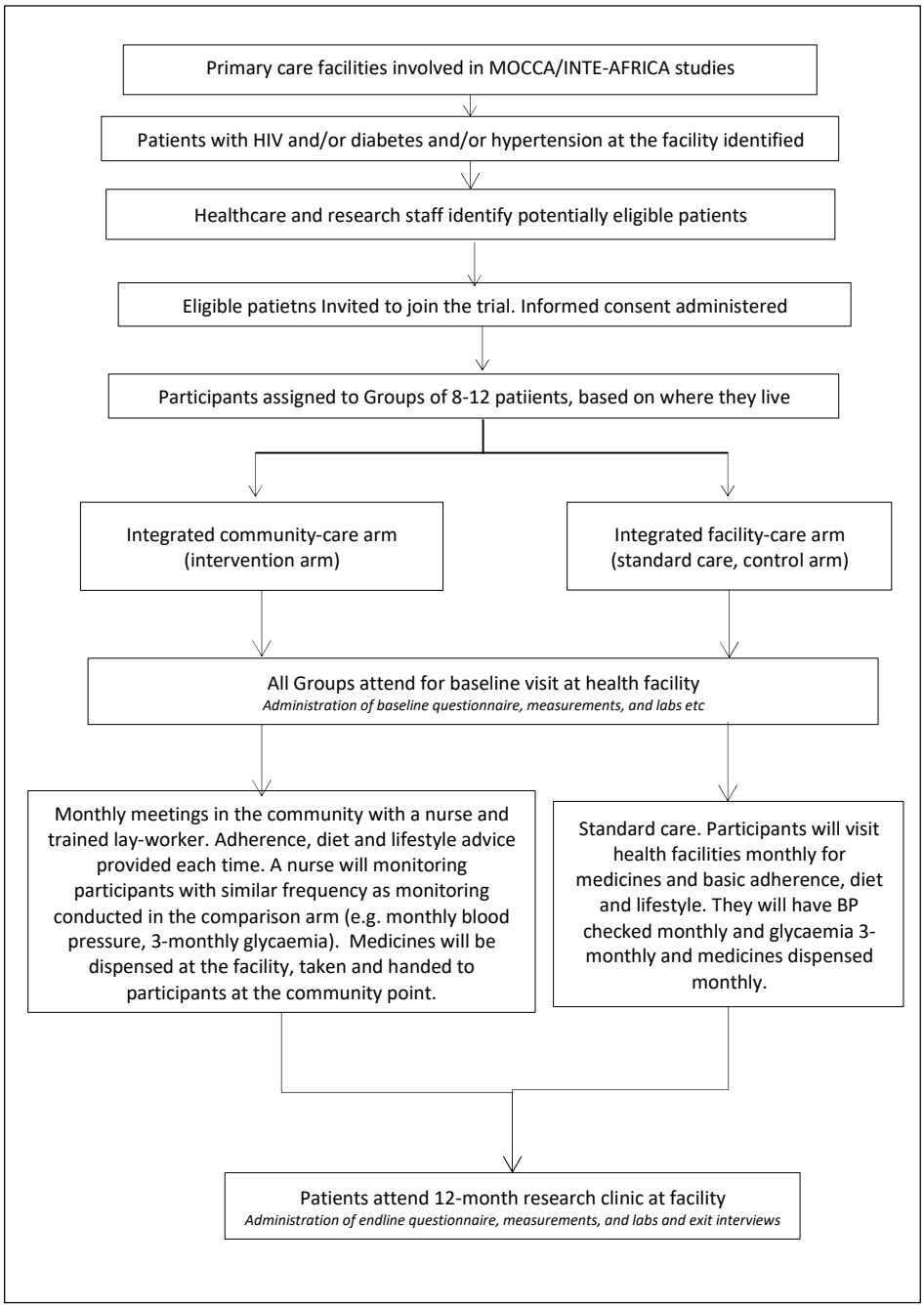
Patients living in the community will be grouped according to their residence in relation to the focal point where they would meet. Our aim will be to select this so that patients can reach it easily, ideally by walking or bicycle.

Assignment of patients to Groups:

At least three persons will be involved in assigning the patients to Groups, comprising a study team member, a field worker/community health worker who knows the area and member of the nursing team who knows the patients. They will assign patients based on their disease and place of residence. We have compiled patients' contact information, including phone numbers. A minimum of two people with each of HIV, diabetes and hypertension will be selected per group. The rest will be patients with a variable mixture of the three conditions. Where there are many patients, we will categorise by age category.

Patients attending the facilities will be given information leaflets and we will display posters also to convey information about the study. They will be asked to consider joining the study at at the health facility. The first meeting of the Group will be held at the health facility for each group. These procedures will be pilot tested before being implemented on a larger scale.

Figure 3. INTE-COMM study schema



Selection criteria

The inclusion criteria into the study will be patients:

- Either diagnosed with HIV or diagnosed with diabetes type 2 or hypertension (or with combinations of these conditions.
- In regular care at the health facility for 6 months or more (i.e. attending routine appointments)
- considered by the clinical team not to have any complications/co-infections or that these are well managed. Also has remained on the same treatment regimen for at least 3-6 months (both the type of medication and dose) and does not require a change in management.
- considered adherent to treatment by clinical team over the last 6 months.
- Adult, age 18 years or older.
- Living within the catchment population of the health facility.
- Planning to remain in the area for at least 6 months.
- Willing to attend for health services in the community.

Exclusion criteria

We will exclude the following patient categories:

- Blood pressure >160/100 mmHg at the current visit (average of 2 readings).
- Blood pressure recorded on more than one occasion as over 180/110 mmHg any time in the last 6 months.
- Fasting glycaemia recorded on more than one occasion as over > 13 mmol/L any time in the last 6 months.
- Complications of diabetes or hypertension that are unmanaged / uncontrolled.
- Any clinical condition that requires health facility management.
- Pregnant women as these require specialist care. However, we will refer patients who become pregnant in the course of the study to the health facility for antenatal care and further management. These patients will be welcome to attend community meetings after delivery.

Data collection

Study participants will be seen by government health care staff who will record basic clinical data on each person. These will be scheduled appointments or when the participant is sick (i.e. self-refers to the health facility). The research team will collate and computerise these data to describe, for example, the frequency and nature of the participants' attendances at the health facilities and at the Group meetings.

The study participants will also be seen by the researchers at baseline (screening and enrolment) and at study end at 12 months follow-up. Using standardised protocols, blood pressure will be measured in the persons with hypertension, and fasting blood glucose in the persons with diabetes at these times. HIV plasma viral load will be measured in the persons with HIV at baseline (or within the last 12-months) and study end. We have considered the research team seeing study participants more frequently to record data but repeated measurement could influence their health behaviour and outcomes.

Sample size

We will compare community care and standard facility-based. Community care will be more accessible to patients and, given that it is delivered in small groups, it will be more personalised. As mentioned above, control of blood pressure and of glycaemia is generally poor. In the MOCCA pilot study, which was done in 10 facilities and over 2,000 participants followed for 6-12 months, 54% of participants with hypertension had good control of blood pressure (BP<140/90 mmHg) and 39% with diabetes had achieved a fasting glucose <7 mmol/L.

We hypothesise that outcomes in the community care model will be superior since a) care and support will be provided close to the home of the patient, b) it will be personalised, delivered by village health worker and a nurse, and c) the reduction in support from clinically qualified staff will be minimised with a nurse working alongside the community health worker. Indeed the purpose of including a nurse was to improve the blood pressure and glycaemia outcomes (i.e. better control than observed in the MOCCA study), as discussed above.

Thus, our calculations are done on a 5% two-sided significance level. In secondary analysis, which will be spelt out in the analytical plan, we will explore equivalence between comparisons.

We assume that 50% of participants in the control arm with diabetes or hypertension will achieve a good level of control after 12 months, that is blood pressure <140/90 mmHg and fasting plasma glucose <7 mmol/L). This is plausible since we will be recruiting people who are in regular care and so should be starting with a better level of control, and patients in both arms will be monitored and supported as per guidelines.

Table 4 shows the sample size calculations for a group randomised trial comparing integrated community care with integrated clinic-based care for control of blood pressure and/or glycaemia. The body of the table shows the total number of clusters needed to achieve 80% power at the 5% two-sided significance level.

Table 4 Sample size calculations for a group randomised trial comparing integrated community care with integrated clinic-based care for control of blood pressure and/or glycaemia. The body of the Table shows the number of groups required in total.

		Assumed proportion with controlled blood pressure or glycaemia in the community care intervention arm		
Group size	**ICC (K)**	**60%** (Absolute diff 10%)	**62.5%** (Absolute diff 12.5%)	**65%** (Absolute diff 15%)
n=4	0.01 (0.20)	210	136	96
n=4	0.02 (0.28)	216	140	98
n=6	0.01 (0.20)	144	92	66
n=6	0.02 (0.28)	150	98	68
n=8	0.01 (0.20)	110	72	50
n=8	0.02 (0.28)	116	76	54

Notes: Assumes proportion with control blood pressure and/or glycaemia is 50% in the clinic-based arm, and a 5% two-sided significance level.

Thus, with 116 groups of 8 persons each with diabetes or hypertension, the trial will have 80% power to detect an difference in absolute rise of 10% (i.e. 50% versus 60% achieving good control in the 2 arms would be statistically significant at the 5% two-sided significance level if the intra-class coefficient is 0.02 or lower). Power will be very high for differences larger than this.

For the HIV viral suppression endpoint, the MOCCA study shows that viral suppression is close to 90%, the UNAIDS target, in this population. Thus, the primary aim is to show non-inferiority with the community-care arm (and secondary analyses will compare superiority).

The non-inferiority margin in trials is often set at 10% (i.e. that the upper one-sided 95% CI of the difference between the control and intervention arm in terms of viral suppression will be within 10%). If we form 116 groups in total, each with 4 participants with HIV, then the trial will have over 80% power or more to show non-inferiority at delta= 8.5%, 7.5%, and 5.5% assuming viral suppression is 85%, 90% and 95% respectively (assumes an intraclass coefficient of 0.02).

Thus, we need a sample size of 116 groups, each comprising 12 persons of which 8 should have diabetes or hypertension and 4 should have HIV. This equates to 1,392 evaluable participants in total. We propose to enrol 124 groups to allow for just over 5% to loss to follow-up in the number of groups. In each of these 124 groups, we will enrol 14 persons to allow for losses to follow-up of just over 10% in the number of participnts. Thus, our target sample size is 1,736 participants. Approximately half of the enrolment will be in Tanzania and half in Uganda. Thus, each country will enrol a total of 62 groups and 868 participants in total. In Uganda, as there is experience of community-based HIV care delivered to groups, we estimate that recruitment will take 2 months. In Tanzania, we will allow for 6-9 months for recruitment.

Pathways to impact

Is the evidence to be generated relevant?

Premature adult deaths from diabetes and hypertension in sub-Saharan Africa are now estimated to be around 2 million a year and rising sharply. One reason for this high death rate is that few people with these conditions (approx. 5-10%) are in regular care, and among these few, the control of blood pressure and glycaemia is poor as our research and that of others has shown. Thus, models of care are needed that both retain patients in care and improve their health outcomes while being cost-effective for health services. In Africa, non-communicable diseases are diseases of poverty.

The research questions that our proposal will address – around evaluation of scale-up of integrated community care - have been formulated by health policy makers and senior health managers working in partnership with researchers. The researchers have helped articulate the ideas from policy-makers and health care providers into research questions and we will provide expertise in research methods. The ideas have also been discussed extensively with patient leaders and civil society members. **Thus, our research is owned by decision-makers and by the users (communities and patients).**

Will the evidence be used by policy-makers? For this proposal, policy-makers in Tanzania and Uganda, supported by senior researchers in those questions, have asked for evidence on:

- efficacy (i.e. how superior or inferior is the proposed intervention of integrated care compared with standard care?)
- costs and cost-effectiveness (i.e. what does it cost and how do the costs compare with the potential benefits)
- acceptability to patients and the health service, and how the scale-up should be done/ modified.

We have work-packages in each of these areas measuring effects on clinical and public health indicators, on health economics and social science. Thus, we will be generating evidence that policy-makers have requested. We are proposing to answer the primary question using a randomised controlled trial, i.e. the gold standard for research studies. The trial is large and simple. It comprises just 2 arms and is designed to provide policy makers, health programme managers, guideline committees and other stakeholders with the clearest evidence of efficacy in as simple a way as possible. The choice of this design is also dictated by policy-makers who have asked for clear evidence that they can use locally.

What is the evidence that policy-makers and patients will buy into this? This depends crucially on the findings, particularly around the costs, benefits and the ease of access to this new integrated community approach. For the last 4 years, patients, civil society organisations, senior health care managers and policy-makers have been working with us, the research group, and the evidence to date shows that in facility-based research settings, the proposed model of care

is both cost-effective and acceptable to patients. Thus far, these stakeholders, including policy-makers, have stayed closely working with the research group. For example, senior national disease control managers have visited our research sites to show support for and provide over-sight to the work (see our website https://www.lstmed.ac.uk/RespondAfrica). They regularly attend our steering committee meetings and participate in all major decisions.

How will we engage with the policy makers, patients, civil society? Our approach to engagement and involvement of these stakeholders has been tried and tested over the last 4 years of working together. We have been and we will do the following:

- We have 3 steering committees: one each in Tanzania and Uganda, and the international steering committee which has representation from all partners and includes independent researchers. These committees include policy-makers, patients, civil society members and senior researchers. They are responsible for strategy.

- We will also communicate through other means, including leaflets, website, short films, community fayres, and workshop/large meetings. We will publish our findings and write briefs for the Ministries of Health.

How will we support transfer of policy to practice. Health policies have already changed in Tanzania and Uganda as our recent review shows (Adeyemi et al BMJ Global Health 2021) and so the policy framework is already in place. The political will is there. The key will be translating policy to practice. We will support health services as follows:

- We will develop the capacity of health care workers to administer tests and train them to train others so that this work may continue after the research finishes
- We will assist governments with documentation needed to support scale up. This will include leaflets and posters giving information and guidelines written with Ministry of Health colleagues on how health care / diagnostic testing should be organised (we are currently doing this, turning our research standard operating procedures into guidelines). We will also derive a set of indicators so that health services can monitor progress of scale up and quality of care long after the researchers have finished and left.

Why now? Health services in Uganda and Tanzania are scaling up integrated care for HIV, diabetes and hypertension and now is the time to modify the intervention and evaluate as they scale-up. Also, our current MOCCA & INTE-AFRICA research projects, which have informed the research plans on community care, are now coming to an end. The research teams are already in place and both us, the health care providers and the public health bodies have the momentum behind us.

Data management and analysis

We have invested considerably in data collection systems. We will create an electronic database using a python-based system, operating on a combination of laptops and tablets. We have used it extensively to collect data from clinical trials (including drug trials) with near 100% accuracy. Finalised data are usually available within 1-2 days of collection.

Data from the trial will be analysed using Generalised Estimating Equations to take account of clustering based on intention-to-treat principle. Primary analysis will compare proportions of patients achieving viral suppression, blood pressure and glycaemic control.

We will calculate costs of health care delivery and costs patients incur to access health care (i.e., societal costs) and link these data to estimates of effectiveness to estimate potential cost effectiveness. We already have substantial costs data from our NIHR programme.

Detailed statistical analyses will be described in the statistical analysis plan.

Ethical considerations

INTE-COMM will conduct the research in accordance with the principles of Good Clinical Practice and MRC ethical guidance on cluster randomised trials (Medical Research Council. Cluster Randomised Trials – Methodological and Ethical Considerations. 2002. https://www.cebma.org/wp-content/uploads/Cluster-randomised-trials-Methodological-and-ethical-considerations.pdf). We are currently conducting large studies on integration as part of the UK NIHR-funded Group on the prevention and management of HIV-infection and non-communicable diseases.

In INTE-COMM, UK partners will request ethics clearance from their institutional ethics committees prior to the start of the scale-up. In Tanzania, the partner will apply to National Health Research Ethics Sub-Committee (NatHREC) for ethics clearance. In Uganda it will be the Uganda Virus Research Institute ethics committee.

INTE-COMM will be monitored by a data safety monitoring committee and a steering committee, which will have representation from independent researchers. Ethics issues will be reviewed by the investigators before we begin and reviewed regularly thereafter, including during each steering committee meeting.

Basic principles. We will be collecting data so that we can determine the effectiveness (including cost-effectiveness) of integrated care. Data collection will be minimal – only essential data will be collected, and focus will be on answering the primary question – i.e. the effectiveness and cost-effectiveness of integrated care. We will ask for written consent from patients (Appendix 2).

All data collected will be treated confidentially. Data will be stored in secure locations.

Computer databases will be encrypted, and data will be anonymised and stored without patient identifiers in accordance with Good Clinical Practice. Secure platforms will be used to transfer data electronically between partners for analyses.

Patients will receive information about the research, including a written information sheet. They will have the right to refuse to participate in the research component or withdraw at any time without affecting their right to care. They will also be able to refuse or withdraw from parts of the research (e.g. interview on aspects of acceptability). All patients will be diagnosed with conventional tests and will receive the same quality of care as current standards.

Randomisation is justified because, given limited prior evidence, there is equipoise about whether the intervention will be more or less effective than usual care. However, it is highly unlikely to cause significant harm. We will monitor deaths, strokes, hospitals admissions and other indicators and these will be analysed by an independent data monitoring committee.

Right to refuse or withdraw: Persons joining the studies will be given information and invited to join if they agree to provide written consent.

Since our research is about chronic conditions affecting older persons, it is unlikely that there will be persons under the age of 18 years coming forward. All persons with diabetes or hypertension (or HIV for the integration with HIV-services) who are aged 18 years or more will be invited to join.

Patients will be free to decline joining the study or to withdraw at any time, without affecting their right to care.

When persons with diabetes or hypertension refuse integrated care: Some persons with diabetes or hypertension will not want to transfer their care to an integrated community care, particularly when NCD services are integrated with HIV services, because of stigma or for other reasons. In these cases, they will be free to continue their care at their current location.

When persons with HIV-infection refuse integrated care: At the health facilities and communities where INTE-COMM will be based (and indeed across Africa), it is the HIV-services that are stronger and generally more accessible than services for other conditions. Few HIV-infected persons have been tested for diabetes or hypertension. Those few (HIV-infected persons) who are known to have diabetes or hypertension, have to go to different clinics at present, which are sometimes located in different health facilities. Thus, integrated care services will likely be hugely popular for HIV-infected persons since for them, integration should mean additional services. However, if there are HIV-infected persons who do not wish to come to the integrated care health facilities for their HIV care for whatever reason, they will be allowed to continue receiving usual vertical care at their current health facility.

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Appendices

Appendix 1: Scoping review summary report

Community-based interventions for the integrated treatment of HIV and Diabetes and/or hypertension in Sub-Saharan Africa: Scoping review summary report

OVERVIEW

The INTE-COMM study will examine whether integrated care of HIV, diabetes (DM) & hypertension (Hyp) can be achieved at a community level in Tanzania & Uganda. However, prior to full testing of such an integrated model of care, the form that this care will take needs to be determined. To achieve this, all potential interventions were initially identified, to inform the development of several future interventions for pilot testing, and then for the most appropriate model to be tested through an RCT. As such, a scoping review was conducted to initially identify all previously used interventions which have either been used, or proposed, to ideally treat patients with HIV and diabetes/hypertension together through integrated care, but more likely through individual care approaches. This document summarises the evidence that was searched to identify such community-based interventions and details for each intervention can be found in Table 1.

METHODS

Three evidence sources were utilised to identify community-based interventions which were either in use, or had been proposed, to achieve integrated HIV & DM/Hyp management and treatments, or for either individually, in any country from Sub-Saharan Africa:

- *Government health policy*:
    - These included the most recent high-level policy documents published by Ministries of Health in Tanzania & Uganda to support healthcare systems in the delivery of care
- *Published research*
    - Non-systematic PubMed searches
- *Ongoing research*
    - Identified from the Global Alliance for Chronic Disease (GACD) website

Though the INTE-COMM study is focused on integrated care of HIV, DM and Hyp at the community level, the novel nature of this objective meant that the identification of such specific interventions was unlikely. As such, the criteria for this scoping review were broader than just an integrated care approach of community-based care for these conditions, but rather identified any reported intervention which was also used at an individual condition level. The rationale to this was that any existing community-based intervention used with conditions individually, has the potential to be adapted to form integrated care in the future. Articles were not excluded based on their study design.

RESULTS

Government policies of Tanzania & Uganda

No specific community-based interventions for the integrated care of HIV & NCDs were reported in any health policy document from Tanzania or Uganda. Regarding health policy documents focusing on NCDs, only strategic health policies were identified. Though these did suggest integrated and differentiated service delivery models to manage NCDs at the community-level in the future, these were typically considered aspirational, with no detail regarding their future design or implementation. The predominant condition for which health policies were identified from these countries were for HIV & AIDS.
HIV & AIDS health policy documents identified from Uganda & Tanzania typically fell into four categories: strategic plans, operational manuals, guidelines, or standard operating procedures. Here, strategic plans offered more information on community-based models of care than provided for NCDs, such as the affirmation that differentiated service delivery models for ART, with community-based distribution, as well as strategies for the support of adherence and retention are crucial, and furthermore, that the scale-up of such services should be achieved through decentralised and integrated care and treatment, but such services would require capacity building for existing CHW.

HIV & AIDS guidelines - Tanzania

Though service delivery through CHW or "peer-based outreach services" were mentioned as community-based models which have shown success in supporting adherence and retention. Only two specific community-based interventions were detailed across guideline and operational documents. These documents provided specific information on the management of stable HIV patients at a community-level. This is proposed though ART refills for stable HIV patients, including **family member or treatment supporter refills** or **community-based ART delivery through mobile outreach**, though the latter is still facility-led. The need for links between facility and community-based care are emphasised, along with the criteria required for both community-based service providers and CHW, including their roles and responsibilities. Finally, details on how Community Based HIV Services can improve ART adherence are provided.

HIV & AIDS guidelines – Uganda

In very much the same way as Tanzania, guideline documents provided details of community-based care. Again, differentiated care and treatment service delivery models for stable clients were recommend in general, with two specific models proposed and detailed. These included **community drug distribution points (CDDPs)**, where clients pick up drugs from a community outreach point, and **community client lead ART delivery (CCLADs)**, where clients form groups from their communities and rotate drug pick-up from the facility or CDDP. A 2017 report which assessed use of CHW in differentiated HIV/AIDS service models reported that the use of community-based interventions, both for individuals and groups, is relatively low compared to facility-based care. Data provided on select endpoints related to CDDP. For clients initiating ART from 2004 to 2009 in the CDDP model, TASO reported 69% retention, 17% died, 6% transferred out and 9% loss to follow up (LTFU). In subsequent related studies CDDP clients, viral load suppression was 93%; LTFU was reported

as 16.5% in the facility arm and 4.28% in the CDDP arm. Finally, two other community-based intervention are mentioned (**adherence counselling** and **Community ART Support Agents (CASA)**), but no further information is provided.

Research

Seventeen individual research articles, from nine different countries across Sub-Sahara Africa (sSA), and five systematic reviews, covering larger geographical areas, were identified from 2007 to 2020. Though most of these research articles examined community-based interventions for individual HIV or NCDs, in contrast to government policies, two did examine methods for integrated care approaches.

Community-based interventions of integrated HIV & NCD care

Two articles examined models of integrated community-based care for HIV with diabetes and/or hypertension. The first of these was Khabala et al (2015), who examined the use of combined **medication adherence clubs (MAC)** in Kenya, demonstrating the feasibility and early efficacy of MAC as a novel group treatment model to care for stable patients in an urban, resource-constrained, informal settlement. Dunbar et al (2018) examined developing the role of **CHW to provide a household model of care** for patients in Malawi, expanding the role of CHWs to focus on the health of entire households, rather than the previous focus only on patients already diagnosed with HIV and TB, incorporating other conditions such as hypertension and diabetes. This study was designed to estimate the effect of the CHW Household Model—as compared with the pre-existing HIV/TB-specific CHW model, primarily examining retention rates across conditions. However, this article is currently only published as a protocol for a stepped-wedge, cluster RCT, so no results exist.

Community-based interventions for diabetes or hypertension

Jeet et al (2017) pooled RCTs that had examined the use of **community health workers** (CHW) in LMICs (though only 2 sSA countries) for treatment of NCDs. They found that while CHW interventions were not very successful in altering individuals' behaviour patterns, modifications in physical parameters, such as systolic and diastolic blood pressure was clearly observed. Community health workers were also able to introduce and sustain a long-term control on HbA1C levels among diabetics, however short-term effects observed were not statistically significant.

Six articles reported the use of community-based interventions in diabetic samples, and four in hypertensive samples. Bobrow et al (2016) examined the same **SMS adherence support messaging system**, though this was tailored for hypertensive (StAR-BP) and diabetics (StAR2D) samples, respectively. Through an RCT they found a small, reduction in systolic BP control compared to usual care at 12-months in the South African sample. However, the RCT examining this intervention in a diabetic sample from South Africa & Malawi is still ongoing and only the protocol is currently available (Farmer et al., 2019). Another study including an electronic intervention was proposed by Vedanthan et al. (2019), who tested a **tailored behaviour communication strategy** to optimise linkage and retention to hypertension care in rural Kenya. A paper and smartphone app format of the intervention were tested against usual care through a three-arm cluster RCT. They found that CHWs equipped with a tailored

behavioural communication strategy and a smartphone-based mHealth tool led to improved linkage to hypertension care, but not statistically significant improvement in SBP reduction among hypertensive individuals, compared with usual care. Ndou et al (2013) examined an intervention for both hypertension and diabetes, examining the effectiveness of **home visits by CHW** through a retrospective case study conducted in South Africa. Their findings suggest home delivery of medication and monitoring by CHWs (rather than nurses) did not worsen control of hypertension. However, the same was not true for diabetes, where the condition was better managed among clinic patients. Pastakia et al. (2017) also examined an intervention in hypertensive and diabetic patients. Their BIGPIC model utilised a **comprehensive microfinance-linked, community-based, group care model** and resulted in 72.4 % of screen-positive participants returning for subsequent care, of which 70.3 % remained in care through the 12 months of the evaluation period. Patients remaining in care demonstrated a statistically significant mean decline in systolic & diastolic BP.
The remaining articles all focused on patients with diabetes, with two examining interventions to support patients and one directly shifting NCD care into the community. Guwatudde et al. (2018) have published a study protocol for the SMART2D trial, comparing facility-only care with integrated facility and community care to improve diabetes outcomes in Uganda and South Africa. Here their community intervention contains a suite of **community mobilisations and support tools** provided by CHW, peer support and a care companion. Through a non-randomised controlled trial, Assah et al (2015) found that **community-based multilevel peer support**, in addition to usual care, significantly improved metabolic control in patients with uncontrolled DM in Cameroon. Finally, a study by Mamo et al (2007) involved a community care programme being developed in rural southwest Ethiopia. This involved **general duty nurses at rural health centres** being trained to provide care for diabetic patients, with regular supervision from the hospital physicians.

Systematic reviews of community-based interventions for HIV

Nachega et al. (2016) conducted a review examining articles which had compared community-based interventions in LMIC (8 sSA countries) to facility-based antiretroviral therapy (ART). They found no statistical difference in optimal ART adherence, virologic suppression, all-cause mortality, and loss to follow-up between these, when the analysis was restricted to RCTs. In the pooled analysis from both RCTs and cohort studies, they report that participants assigned to community-based ART had significantly higher rates of retention in care than those in facility-based ART at the end of follow-up.

Kanters et al. (2017) examined a range of interventions assessed through RCTs to improve adherence to ART and viral suppression in low- and middle-income countries (LMIC). They found the supportive strategies of **peer support, two-way SMS text messaging, and counselling, and behavioural strategies** improved adherence compared with standard adherence support. However, in general, the effects of even the most effective intervention were slight, but adherence did seem to increase when effective interventions were combined. No intervention improved viral response in LMIC samples. Penn et al. (2018) also examined whether supportive interventions could increase retention in care for patients on ART in LMIC. They found that community-based interventions featuring a **treatment or adherence supporter with home visits** were effective in improving retention in care in resource-limited settings, but evidence quality was generally low to moderate. Furthermore, most studies showed a significant improvement in retention, and significant decrease in the

combined outcome of LTFU or mortality.

The three other HIV reviews were focused on sub-Saharan Africa populations. Decroo et al. (2013) in 2013 reviewed the literature for **approaches and impact of engaging lay people in ART delivery** (including volunteers, community health workers (CHWs) and PLWHA). The found that community ART programs made treatment more accessible and affordable. However, to achieve success some major challenges needed to be overcome: first, community programs need to be driven, owned by and embedded in the communities. Second, an enabling and supportive environment is needed to ensure that task shifting to lay staff and PLWHA is effective and quality services are provided. More recently, a rapid review by Chimatira and Ross (2020) pooled information on the effectiveness of **community-based antiretroviral therapy initiation** (CB-ARTi). From six articles (four RCTs & two cohort studies) there was evidence that CB-ARTi can increase linkage to ART, retention in care and viral suppression rates, and is possibly not inferior to facility-based healthcare. Finally, Nyoni et al. (2020) examined the effectiveness of **treatment supporter interventions (TSI)** in ART adherence and viral suppression across facility-based and community-based TSI interventions. From the pooling of data from 10 RCTs and 6 cohort studies, they found that Community-based TSIs (comprising either partners, friends, family members, trained community health workers, or HIV positive peers) were significantly associated with viral load suppression, while facility based TSIs were not.

Community-based interventions for HIV

Five articles were identified which examined community-based interventions for HIV in African countries. These interventions took three general formats; **drug collection groups, home-visits, and multifaceted support packages**. Similar to the HIV policies from Tanzania & Uganda. Decroo et al. (2017) examined the role of groups of patients who coordinated to collect ART medication. They found that patients in **community ART groups** from Mozambique had substantially better retention in care at 12 & 24 months compared to those in individual care. Two RCTs examined the benefit of enhancing HIV care with home visits by non-clinical support staff. Jaffar et al. (2009) examined the use of **home-based HIV care**, with lay workers delivering ART and monitoring patients, finding that this home-based HIV-care strategy was as effective as a nurse-led and doctor-led clinic-based strategy for prevention of virological failure, mortality, and other adverse outcomes. Lubega et al. (2015) took a similar approach, finding that compared to usual care, additional monthly follow-up home visits by **community supports agents** more than doubled the retention of PLHIV in pre-ARV care in rural Uganda. Finally, two articles consider multifaceted home and community-based care packages in addition to standard care. McBain et al. (2017) examined the effect of a **comprehensive HIV program**, which extended usual HIV care, in the Neno District of Malawi, by providing additional community-based elements to usual care. They found that 1-year survival rates among new enrolee's exceeded national standards by 9.1 percentage points, and that the model was cost effective. Rich et al. (2012) also examined the role of a **community-based ART program** in HIV patients in rural Rwanda, finding that this intervention provided excellent outcomes in 24-month retention in care.

GACD website

Three relevant projects were identified on the GACD website (which did not yet have any

attached publications). Two of these studies used samples from Tanzania, the third from Eswatini. All three proposed the use of some form of **mHealth/SMS intervention to support CHW** in managing or treating patients with diabetes or hypertension. Four other GACD projects are included in the above 'research' section of this document.

SUMMARY

Through the compilation of research and grey literature evidence, this document outlines a variety of community-based interventions which exist (or are planned) to support treatment of patients with HIV, diabetes or hypertension, either in individual African countries, or more widely across sub-Saharan Africa or LMIC. The majority of these works examined interventions on individual conditions, demonstrating the dearth of understanding regarding interventions for the integrated care of patients at a community level.
Regarding published research evidence, several systematic reviews have already been conducted to examine the strength of a number of interventions in HIV samples in either LMIC or sub-Saharan Africa countries. Research into community-based interventions for diabetes of hypertension is more limited. Across this body of literature, a wide variety of interventional designs were reported, with few being assessed again in different populations. However, we were able to categorise community-based interventions into six general design groups, including those i) improving access to medications (specifically ART), ii) providing treatment support programmes, iii) multifaceted support programmes, which are comprised of several interlinking interventions iv) home visits from community health workers, v) support via SMS text messages and vi) differentiated care. Where research had compared patient outcomes between community and alternative care (i.e. usual care), the majority found that outcomes were either improved, or at least no worse than the standard care, though study design and quality varied across this research. Across the research literature there is also some suggestion that a suite of interventions may be more effective than a single measure.

From a range of government policies from Tanzania & Uganda, four community-based interventions are recommended for the treatment of patients with HIV and are accompanied by clear and detailed methods for their implementation in practice. These involve improving patient access to ART medication (and so crosses over with the research category above). Though the importance of integrating HIV care with other conditions (including NCDs) is highlighted as important for future care provision in several health strategy documents, no specific community-based interventions are detailed.

Of the ongoing GACD projects without publications, all focused on the use of mHealth methods, either used or supporting CHWs to improve multiple aspects of hypertension or diabetes care based in the community. This appears to be a developing area relating to NCD.

In conclusion, there is currently no clear evidence for a community-based model of integrated HIV & NCD care. However, there is policy and research evidence for several different models of effective community-based care for HIV, and research (though limited) for hypertension or diabetes care in the community. One approach may be to adapt and pilot one (or several) of these models for INTE-COMM patients with HIV & diabetes or hypertension, another approach is to consider one of the several community-based interventions which are being developed for diabetes or hypertension and adapt this accordingly.

Table 1: Community-based interventions reported across all sources

Author	Community-based intervention and design details	CD	NCD	Source	Design
	MEDICATION ACCESS				
Tanzania MoH	Family Member or treatment supporter refill One member of family collects refills for several family members	HIV	-	Policy	N/A
Tanzania MoH	Community-based individual ART delivery through mobile outreach • Occurring at fixed location, • ARV refills can be collected by family member, designated person etc. • These are distributed by health professional	HIV	-	Policy	N/A
Uganda MoH	Community client lead ART delivery (CCLADs) Clients form groups from their communities and rotate drug pick-up from the facility or CDDP	HIV	-	Policy	N/A
Uganda MoH	Community Drug Distribution Points (CDDPs) Clients pick up drugs from a community outreach point	HIV	-	Policy	N/A
Decroo et al. (2017)	Community ART groups • Peer groups members take turns to travel to the clinic to collect monthly ART refills for all group members	HIV	-	Research	Retrospective cohort
Decroo et al. (2013)	Home- or community-based ART delivery • Home-based ART delivery by non-clinical individuals	HIV	-	Research	SR
Chimatria	Community-based antiretroviral therapy initiation (CB-ARTi) • CB-ARTi programmes that start ART in communities in comparison with the current standards of care	HIV	-	Research	SR (Narrative synthesis)
Nachega et al. (2016)	Community-based ART delivery • Articles were included with interventions relating to: 1. home-based interventions (e.g., friends or family-centered approaches); 2. peer- or HIV patients-led interventions; community ART distribution points (with or without involving primary level formal or informal health facilities);	HIV	-	Research	SR (Meta-analysis)

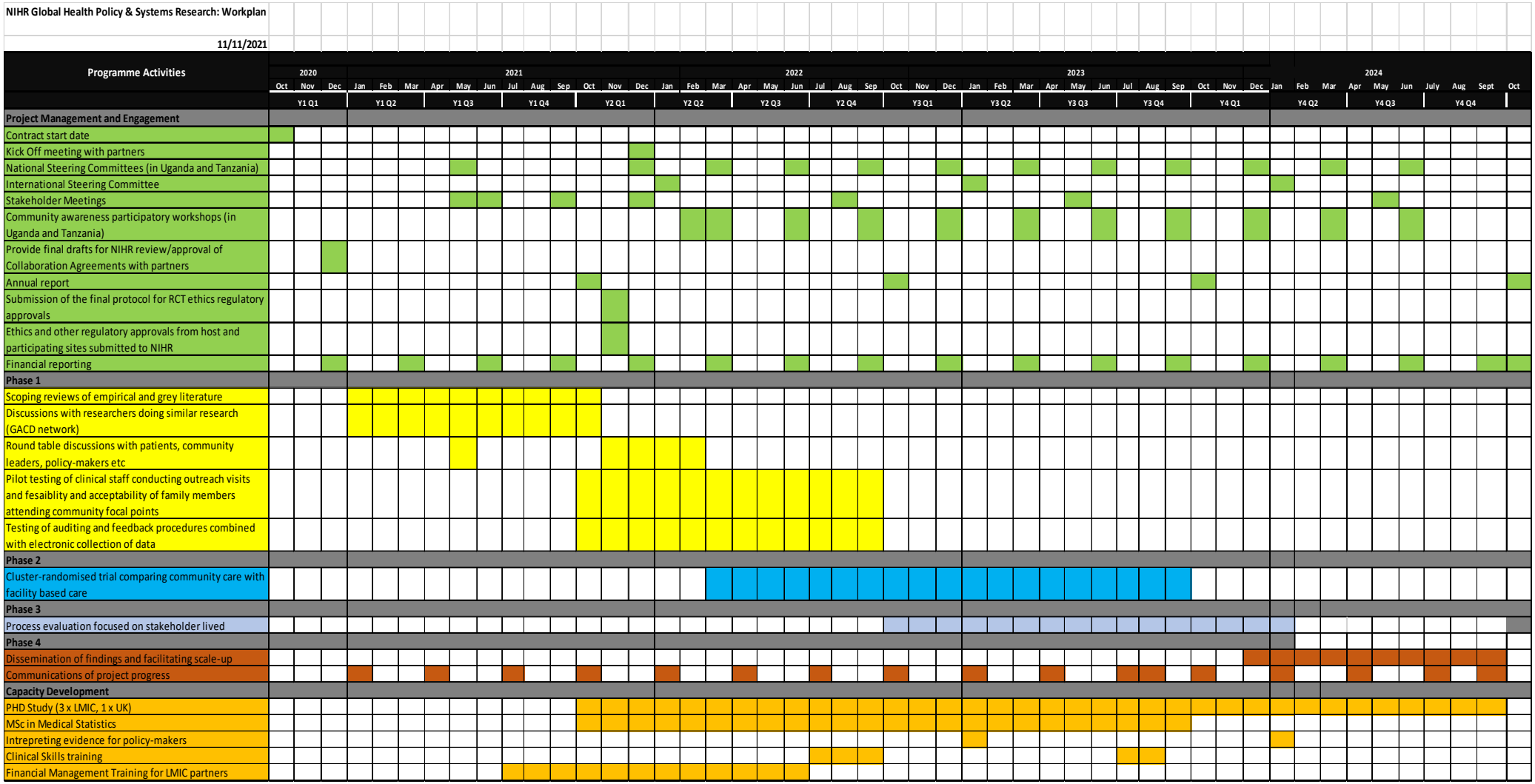
	3. community-based ART adherence clubs (with or without involving primary level formal or informal health facilities); 4. community ART groups (CAGs)				
Penn et al. (2018)	Supportive interventions to improve retention on ART • Four types of interventions: 1. directly observed therapy plus extra support ("DOT-plus"), 2. community-based adherence support, 3. adherence clubs and 4. extra care for patients with low CD4 count	HIV	-	Research	SR
	TREATMENT SUPPORT PROGRAMMES				
Nyoni et al. (2020)	Treatment Supporter interventions • Evaluated the effectiveness of treatment supporter interventions (TSI) in improving ART adherence and viral suppression • TSI included partners, friends, family members, trained community health workers, and HIV positive peers	HIV	-	Research	SR & MA
Khabala et al. (2015)	Medication Adherence Clubs • Nurse-facilitated • Mixed groups of 25–35 stable hypertension, diabetes mellitus and/or HIV patients Meet every 3 months to confirm their clinical stability, receive a brief health talk, and receive medication.	HIV	DM Hyp	Research	Retrospective descriptive study
Assah et al (2015)	Community-based peer support • subjects underwent peer support intervention through peer-led group meetings, personal encounters and telephone calls	-	DM	Research	Non-randomised controlled trial
	MULTIFACETED SUPPORT PROGRAMMES				
McBain et al. (2017)	Comprehensive HIV program 1. Four home & community components added to traditional clinic-based, ART model of care 1. HIV-specific community health workers 2. Social support program	HIV	-	Research	Retrospective cohort

	3. Nutritional support program 4. Community support initiative				
Rich et al. (2012)	Community ART program • psychosocial support • directly observed ART delivered by CHWs, • ongoing HIV education, • nutritional assistance for 10 months, • a travel allowance for routine visits, • comprehensive integrated medical care, including diagnosis and treatment of TB	HIV	-	Research	
Pastakia et al. (2017)	Bridging Income Generation with Group Integrated Care (BIGPIC) model • Comprehensive microfinance-linked, community-based, group care model • Contextualized care delivery model designed to address the unique barriers faced in rural settings. This model emphasizes the following steps: 1. find patients in the community, 2. link to peer/microfinance groups, 3. integrate education, 4. treat in the community, 5. enhance economic sustainability and 6. generate demand for care through incentives.	-	DM Hyp	Research	Prospective cohort study
Guwatudde et al. (2018)	SMART2D - Comparing facility-only care with integrated facility and community care Community-based care included (1) community mobilisation, (2) strengthen the supportive environment (3) community extension (i.e., linkage between facility and community)	-	DM	Research (Protocol)	Adaptive implementation cluster RCT
	CHW HOME VISITS				
Lubega et al. (2015)	Community Support Agents	HIV	-	Research	RCT

	• CSAs are influential community volunteers or experienced ART clients. • Patient were newly screened PLHIV • In additional to standard care, patients received monthly home visits by a CSA for a 2-hour counselling session and reminder to go for pre-ARV care.				
Dunbar et al (2018)	Integrated household model of care • In the new Household Model, each CHW will be responsible for around 20–40 households • Visiting monthly, with more frequent visits to households with members enrolled in chronic clinical care. o During home visits, CHWs are responsible for case finding through education o screening for common conditions, including STIs, TB, HIV and paediatric malnutrition. • They will provide support for linkage to care for symptomatic clients, along with ongoing support and accompaniment for patients in care, including adherence support, psychosocial support and tracking of missed patient visits.	HIV	DM Hyp	Research (protocol)	Stepped-wedge, cluster RCT
Vedanthan	CHW using tailored behavioural communication strategy • CHW was instructed to engage in behavioural, clinical, and environmental assessments, followed by a tailored behavioural and motivational engagement, • Intervention designed to help facilitate linkage to care • Intervention was tested both as paper-based or smartphone-based • Smartphone-based arm had addition of real-time decision support and data entry	-	Hyp	Research	3-arm cluster RCT
Jeet et al (2017)	Community Health Workers • CHW delivered NCD primary prevention interventions	-	DM Hyp	SR	Meta-analysis

	• primary responsibilities CHW included health promotion, treatment adherence and follow ups				
Ndou (2013)	Home visits by CHW • Home delivery of medication and monitoring	-	DM Hyp	Research	Retrospective case study
	SMS SUPPORT				
Bobrow et al. (2016)	SMS to support treatment adherence • Adults with High Blood Pressure • Information-only or interactive personalized SMS text-messages were sent at weekly intervals • Messages designed to address a range of common issues with adherence to and persistence with treatment • Participants allocated to the interactive adherence support could also respond to selected messages, which generated automated responses	-	Hyp	Research	RCT
Farmer et al. (2019)	SMS for improving health outcomes and medication adherence • Brief automated SMS text messages • Trial participants allocated to the intervention group received specifically designed text messages, • Content of these including motivational and educational messages. • They also received prompts (ie, reminders) about medication collection with timing personalized by the information collected about all participants at the baseline visit, from the clinic and pharmacy attendance. Messages were sent three to four times a week for a period of 1 year.	-	DM	Research (protocol)	RCT
	DIFFERENTIATED CARE				
Mamo et al (2007)	Nurses at rural health centres trained to provide NCD care • A senior nurse took charge of the clinic and helped train the nurses and health officers from nearby health centres • Throughout the programme, specialist care and education of nurses has been given		DM	Research	

Appendix 2: INTE-COMM full programme Gantt chart



Appendix 3: INTE-COMM patient information sheet and consent form