

**AN EVALUATION OF STRATEGIES TO ACCELERATE ENTRY-INTO-CARE
FOLLOWING HIV DIAGNOSIS AMONG ADULTS IN GAUTENG AND
LIMPOPO PROVINCES, SOUTH AFRICA**

Short title: Thol'impilo: Bringing People into Care

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STUDY OVERVIEW

Background

Mortality remains high among individuals with HIV in South Africa largely due to low CD4 at initiation of combination antiretroviral therapy (cART) or failure to initiate cART altogether. The problem of advanced HIV at the time of entry-into-care persists despite increases in CD4 count initiation thresholds and higher CD4 counts among individuals testing HIV positive at HIV counseling and testing services (HCT). A reason for the discord between CD4 at HCT and CD4 at cART initiation is a failure to effectively link people who test positive into HIV care; less than half of individuals testing HIV positive enter HIV care within 3-6 month of HIV diagnosis. However, not only do these delays increase HIV associated mortality, delays from testing positive to entry-into-care for HIV also reduces the ability of test-and-treat strategies to reduce HIV transmission through HIV treatment.

Objectives

The main objective of this study is to compare the effectiveness of combinations of three patient-oriented strategies, compared to the standard of care, to increase the proportion of patients who enter-into-care for HIV within 90 days of testing HIV positive.

Study design

We are proposing an open (non-masked) individually-randomized implementation science evaluation of the effectiveness and cost-effectiveness of combinations of three strategies to increase timely entry-into-care for HIV compared to the standard of care. Participants will be randomly assigned to one of four arms to increase timely entry into care: (1) standard of care, (2) point-of-care CD4 and transport assistance, (3) point-of-care CD4 and care facilitator and (4) point-of-care CD4 only. We require 560 participants per arm, and to allow for loss from moving away from the study area or withdrawal from the study, we propose a sample size of 625 per arm for a total of 2500 subjects. Study activities will be conducted over a period of 3 years, from 12 July 2012 to 11 July 2015.

Study setting

The proposed project will be built onto the current community-based HCT (mobile and fixed) services offered by Aurum. We plan to include six HCT teams, 3 operating in Ekurhuleni District (Gauteng Province) and 3 in Limpopo. The HCT units serve peri-urban townships and informal settlements, rural farm workers, and both urban and rural communities

Significance

The proposed project takes an innovative and comprehensive approach in targeting each of the key entry-into-care barrier domains. In addition, it will provide critical effectiveness, costing and cost effectiveness data to inform policy. These results will be highly relevant to the Government of South Africa in setting policy to achieve specific care, cART, and HIV prevention goals set out in the 2012-2016 South African National Strategic Plan.

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LIST OF ACRONYMS

ARTAS	Antiretroviral Treatment and Access to Services
ATM	Automated Teller Machine
cART	Combination Antiretroviral Therapy
CI	Confidence Interval
CREATE	Consortium to Respond Effectively to the AIDS/TB Epidemic
CRF	Case Report Form
CROI	Conference on Retroviruses and Opportunistic Infections
CRT	Cluster Randomised Trial
DoH	Department of Health
EQA	External Quality Assurance
GPS	Global Positioning Systems
HIV	Human Immunodeficiency Virus
HCT	HIV Counseling and Testing
IAS	International AIDS Society
IC	Informed Consent
ICER	Incremental Cost-effectiveness Ratio
IRB	Institutional Review Board
MRC	Medical Research Council
NHI	National Health Insurance
NSP	National Strategic Plan
OR	Odds Ratio
PIS	Patient Information Sheet
PMP	Program Management Plan
POC	Point of care
QA	Quality Assurance
R	South African Rand
RNA	Ribonucleic Acid
SANAC	South African National AIDS Council
SASSA	Social Security Agency of South Africa
SOC	Standard of Care
STI	Sexually Transmitted Illnesses
TB	Tuberculosis
USAID	United States Agency for International Development
USD	United States Dollar
UNAIDS	Joint United Nations Programme on HIV/ Acquired Immune Deficiency Syndrome
WHO	World Health Organisation

I INTRODUCTION

I.1 Background

I.1.1 The delay between HCT and cART initiation

The delay between HIV diagnosis and entry-into-care for HIV must be decreased to maximize the potential impact of combination antiretroviral therapy (cART) to reduce mortality and prevent HIV transmission. When initiated early in the course of HIV disease (prior to symptomatic HIV and low CD4 counts), cART markedly reduces HIV-associated mortality, restores life expectancy, and reduces HIV transmission (Mills *et al.* 2011a;Cohen *et al.* 2011;Mills *et al.* 2011b). Furthermore, success of HIV testing and treatment (treatment-as-prevention) as part of strategy to prevent HIV transmission depends on regular HIV testing and a high uptake of cART services promptly after HIV diagnosis. At present, long delays between testing and initiation of treatment are undermining both the health and prevention goals of HIV care. Delays between HCT and entry-into-care for HIV reveal opportunities for further intervention to prevent HIV transmission and reduce HIV-related mortality.

Current intensive HIV counseling and testing (HCT) efforts in Africa - including the ambitious and successful 2011 campaign of the Government of South Africa to perform 15 million HCT sessions or 30% of the total population - have resulted in earlier HIV diagnosis among a large fraction of people living with HIV (Government of South Africa, 2012). The rapid expansion of cART services in South Africa (Cornell *et al.* 2009) and elsewhere in resource-limited settings have made treatment widely available. However, only 30-60% of HCT patients enter care within 6 months of testing HIV positive (Rosen *et al.* 2007), with the rest dying prior to entry-into-care or starting cART only with symptomatic HIV and a low CD4 count. Delays between HIV diagnosis and cART initiation are further reflected by the median CD4 count at cART initiation (100-150 cells/mm³) and minimal change in CD4 count at cART initiation over the past several years, even as criteria for cART initiation in South Africa have been adjusted upward from <200 cells/mm³ to <350 cells/mm³ (World Health Organization 2010;Department of Health 2010). In contrast, the median CD4 among persons testing HIV positive at HCT is much higher: 350 cells/mm³ in several studies (Govindasamy *et al.* 2011; Ramkissoon *et al.* 2011; van *et al.* 2010) and 777 cells/mm³ in the Aurum HCT program (unpublished data). HCT is successfully identifying people living with HIV in South Africa, and treatment programs are available to provide care, but newly diagnosed individuals are failing to enter care.

Even with HCT and HIV care and treatment widely accessible, disconnect between these services has resulted in a failure to link HIV-diagnosed persons from HCT to HIV care and treatment. Thus, along with HCT and HIV care and treatment, a third service – an entry-into-care system – is essential to achieve timely entry-into-

care following HCT (Figure 1). An integrated system to connect HIV-diagnosed individuals into HIV care and treatment is needed in order to maximize the impact of cART on mortality reduction and transmission prevention.

1.1.2 The South African National Strategic Plan

The South African National Strategic Plan on HIV, STIs, and TB 2012-2016 (NSP) advocates for comprehensive evidence based programmes to achieve *better links between testing and treatment sites* with a specific target of initiating at least 80% of ART eligible patients on ART (South African National AIDS Council 2011). The following are additional specific goals that are relevant to retention in the HIV care continuum:

1. Ensuring that everyone in South Africa tests voluntarily for HIV and is screened for TB annually, *and* subsequently enrolls in relevant wellness, care, treatment, and support programmes
2. Creating well-linked services for HCT to assist in expediting initiation of cART.
3. Reducing disability and death resulting from HIV and TB through universal access to HIV and TB screening, diagnosis, care and treatment.
4. Evaluating and validating new diagnostic technologies, particularly point-of-care technologies appropriate for low-resource environments

A dominant theme in the Government of South Africa's National Strategic Plan for 2012-2016 is bridging the barrier between testing (for HIV or TB) and initiating treatment, the proposed research directly supports this objective.

1.1.3 Entry-into-HIV care system

Designing a system to connect HCT to HIV care and treatment requires an understanding of the barriers and facilitators to entry-into-care. Several steps must be traversed by the HIV-diagnosed patient who is in need of care; some of these steps have been described in the literature and are illustrated in Figure 1:

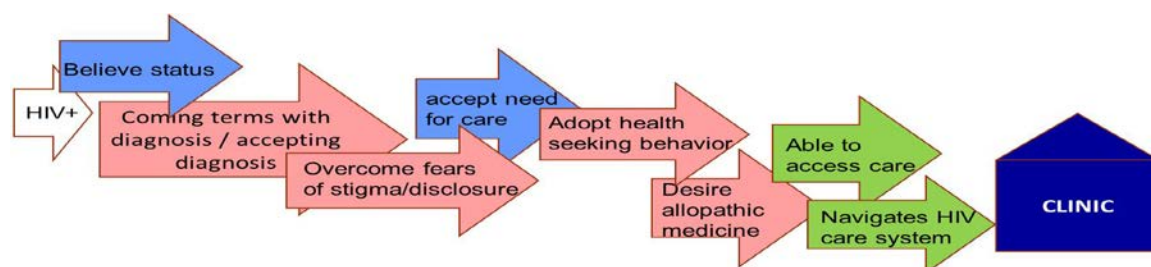


Figure 1.1: Steps in the pathway from HCT to entry-into-care for HIV

The above steps can be grouped into three independent modifiable domains: (1) health perception, (2) acceptance and self-efficacy (personal barriers), and (3) structural barriers (Figure 2).

1. Health Perception

Several studies have found an association between disease-specific knowledge and awareness and entry-into-care for HIV. For example, individuals who had a family member or friend with HIV had a 30% increase in cART initiation (Bassett *et al.* 2009). Symptomatic HIV-infected persons are also 60-80% more likely to access HIV care and treatment than those who are asymptomatic (Faal *et al.* 2011; Marcellin *et al.* 2009; Jani *et al.* 2011; Losina *et al.* 2010). Knowledge of CD4 count, independent of symptoms, is also associated with increased entry-into-care (Faal *et al.* 2011). In addition, this association between health care seeking and disease specific knowledge is well described for other diseases such as myocardial infarction and heart failure (Goldberg *et al.* 2002; Saczynski *et al.* 2008; Nguyen *et al.* 2010). POC CD4 testing will provide a starting point for disease staging and education for the participant. However, we acknowledge overlap between health understanding and acceptance of a diagnosis and willingness to seek care. The latter are addressed in “personal barriers.”

2. Personal Barriers

Multiple models of the patient’s journey to seeking health care have been described. One aspect of this journey is gaining appropriate knowledge of the disease process as addressed in the “health perception” component. Another aspect is coming to terms with the diagnosis, developing an approach to health self-efficacy, and overcoming fears and stigma concerns to actually seek care. A simple and applicable model to coming to terms with a diagnosis and being willing to seek care is the Stages of Acceptance Model. This model describes phases in an individual’s acceptance of their medical condition and willingness to seek care (Kubler-Ross 2005). The process of transitioning between these stages differs for each person and may vary by context.

In South African, stigma and fear of disclosure of HIV status are especially significant barriers to health care seeking. Evidence from studies among HIV-infected women suggests that disclosure of HIV sero-status is linked to and can result in increased social support; the downstream effect is more willingness to seek health care. In a study of a South African cohort, patients who disclosed their HIV status were 1.57 times more likely to register at an HIV facility than patients who did not disclose (95% CI: 1.00-2.48) (Govindasamy *et al.* 2011; Ochieng-Ooko *et al.* 2010). Family size and marital status have also been found to be associated with entry-into-care (Lessells *et al.* 2011). Less explored in resource-limited-settings are the effects of mental illness or substance abuse on entry, however, these are well described personal barriers to HIV care in other settings (Blashill *et al.* 2011).

The care facilitator will specifically address personal issues, assist with progressing through stages or acceptance, and provide support for disclosure. However, we acknowledge that specific education from the care facilitator may also affect health perception.

3. Structural barriers

Despite efforts of the South African government to decentralize ART delivery and make it more accessible, patients may still need to travel considerable distances from places of residence to facilities providing HIV care and treatment. The direct costs of traveling to health care facilities, opportunity costs from lost wages, and costs of child care (if needed) are barriers to accessing care; these costs can represent a substantial proportion of a household budget, and can add up, as multiple visits may be needed for CD4 testing, HIV staging, and diagnostic evaluations for TB and other opportunistic illnesses. Transport costs to HIV care facilities compete with other more immediate responsibilities (e.g. housing, food) and have been consistently reported in South Africa and elsewhere in Africa as barriers to entering and remaining in care. In one study, patients who lived greater than 10 km from the HCT site were 1.37 times (95% CI: 1.11-1.71) less likely to return for collection of results than those who lived closer (Losina et al., 2010). In another study, patients referred to treatment sites >15 km away from the site where they received HCT compared to those who received treatment at the same site, were less likely (OR=0.35; 95% CI; 0.18-0.71) to initiate cART within a year. Findings from Malawi showed that higher cost of transport was associated with failure of entry-into-care (Zachariah *et al.* 2006).

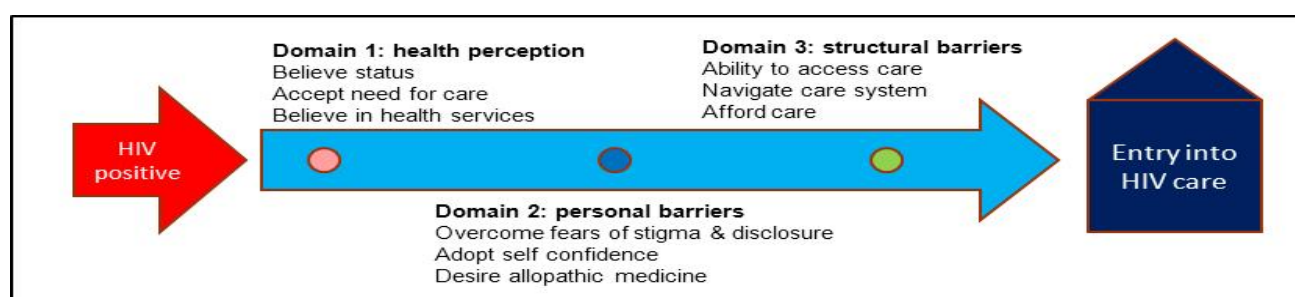


Figure 1.2: Modifiable domains impacting entry-into-care for HIV

1.1.4 Studies assessing approaches to increasing entry-into-care

Findings from studies in the US and southern Africa, with the latter being small pilot studies, provide hopeful data for entry-into-care interventions.

1. Care facilitation

- A study conducted in the United States directly addressed personal barriers to entry-into-care through a care facilitation approach. In that study, patients were randomized to either care facilitation or standard of care soon after HIV diagnosis. Care facilitation increased entry-into-care within 6 months of testing HIV positive from 60 to 87%; when the intervention started soon after HIV diagnosis entry-into-care was over 90% (Gardner *et al.* 2005). The approach was a time-limited intervention of “strengths-based” care facilitation. This is an approach developed from the field of social cognitive theory and borrows from theories of empowerment and self-efficacy (Lee *et al.* 2009). In practice, the care facilitator assists the

client in identifying personal strengths and then applying these strengths to solving problems in manageable chunks. For example if a participant has identified being good at cooking as a strength and lack of income as a barrier to entry-into-care, a care facilitator may guide the participant to use cooking as a possible avenue to income generation as a first step in the entry-into-care process. Given the importance of disempowerment, stigma, and disclosure as perceived barriers to care in South Africa, we believe that this may be a powerful model to apply to South Africa.

2. Point-of-care (POC) CD4 testing with results provided during post-test counseling

- In a small single site trial in South Africa, comparing immediate CD4 testing and provision of results to the standard of care, a 40% increase in patients entering care after HCT was observed in the POC CD4 compared to the standard of care group (relative risk=1.4; 95% CI: 1.08-1.84) purely based on having received CD4 results and education of the meaning of those results at the time of HCT (Faal *et al.* 2011).

3. Transport allowances

- A pilot programme in Tanzania that provided transport allowances and volunteer patient escorts to assist with travel to HIV care facilities achieved a 70% increase in entry-into-care for HIV (Nsigaye *et al.* 2009).

These trials from the United States and Africa provide evidence that reproducible targeted interventions can increase timely entry-into-care. However, several limitations preclude generalized adoption. Limitations of these studies include either small size and limited generalizability (CD4 and transport studies) or a different cultural context (linkage manager in the United States), as well as an absence of cost effectiveness studies needed to inform policy. An evaluation of interventions addressing each of the modifiable domains related to entry-into-care is urgently needed to provide cost effective solutions that may bridge the gap between HCT and HIV care and treatment.

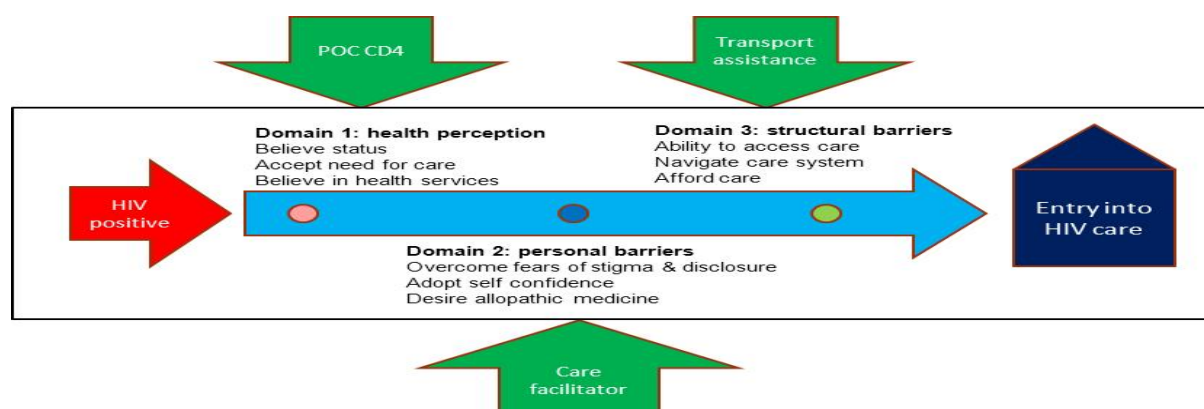


Figure 1.3: Proposed point of action for the three interventions

1.2 Study hypothesis

Patient-oriented strategies that target specific barriers to entry-into-care will shorten time to HIV care entry and increase the proportion of patients entering care within 90 days of testing HIV positive.

1.3 Rationale of the study

It has been well documented that combination antiretroviral therapy (cART) reduces premature mortality and improves quality of life (Mills et al. 2011a). In addition, population level studies and mathematic modeling suggest that high cART coverage can reduce onward transmission. However, despite intensive HIV counseling and testing (HCT) campaigns in South Africa, entry-into-care for HIV following testing is low with fewer than half of tested individuals enrolling in care within 3-6 months of testing (Rosen & Fox 2011). Currently, South Africa lacks a robust and properly functional system to link patients who test HIV positive into HIV care. Mechanisms to increase timely entry-into-care are urgently needed to reduce HIV-associated mortality and to decrease HIV transmission.

The Aurum Institute runs a large volume HCT program that consists of mobile and fixed HCT units serving urban and rural populations. Between January 2009 and September 2011, 120,340 patients underwent HCT (unpublished Aurum data). Overall 14.3% tested HIV positive (17,208 HIV positive tests); for whom the median CD4 was 777cells/mm³ (interquartile range: 610-984 cells/mm³). All patients who tested positive were referred to HIV care; however, specific facilitation for care entry was not provided and actual entry-into-care was not ascertained. Interestingly, at both Aurum HCT units and Aurum partnered Department of Health units, it is common for patients who test positive to return to HCT counselors for informal counseling and guidance on access to care – which suggests an unmet need for a formal care facilitation approach.

Within the Aurum HCT program we assessed mortality following HCT by linking client national identification numbers with the Department of Home Affairs vital statistics registry, and we found that testing HIV positive was associated with a 10-fold increased risk of dying within 6 months of HCT (odds ratio 0.10; 95% Confidence Interval (95% CI): 0.04-0.23), compared with testing negative (unpublished Aurum data). It is plausible that some of these deaths could have been averted with an entry-into-care system. Importantly, patients receiving HCT services must accept follow-up after HCT if the program is to achieve reductions in HIV-related mortality and HIV transmission. In a separate ongoing qualitative study of Aurum HCT service, more than 80% of patients testing HIV positive have agreed to follow-up contact while approximately 84% of all Aurum HCT clients who test HIV positive agree to follow-up contact at the time of testing. The Aurum HCT program with a large number of positive diagnoses and willingness of clients for post-HCT follow-up makes it an ideal setting to evaluate innovative strategies to increasing timely entry-into-care for HIV.

1.4 Potential use of study findings

1.4.1 Usability

The proposed project takes an innovative and comprehensive approach in targeting each of the key entry-into-care barrier domains. In addition, it will provide critical effectiveness, costing and cost effectiveness data to inform policy. These results will be highly relevant to the Government of South Africa in setting policy to achieve specific care, cART, and HIV prevention goals set out in the 2012-2016 South African National Strategic Plan. In addition, the results may be valuable to inform universal HCT and access to treatment program implementation.

1.4.2 Sustainability

A first step in any implementation science project is to demonstrate the effectiveness of an approach. However, feasible implementation and long-term sustainability must be considered as part of the design of the intervention. These depend on effectiveness, cost, cost effectiveness when compared to alternative approaches, and government policy plans. We have developed three interventions that, we believe, can be implemented for a cost that is lower than the annual cost of antiretroviral therapy (currently affordable by the Government of South Africa). In addition, crucial components of the study are the detailed costing and cost effectiveness analyses. These analyses will provide concrete data for health programming budget considerations and policy making. Furthermore, mathematical modeling of long-term outcomes of the intervention will add to the comparability of the impact of the studied interventions to other health care interventions. However, specific policy decisions are best left to Provincial and National Department of Health personnel.

In order to provide data to Government of South Africa policy makers during the study and to facilitate adoption should the interventions prove successful, we will liaise with District, Provincial, and National Department of Health officials during the study implementation and result dissemination processes. At the District and Provincial levels this will occur through the ongoing government-NGO taskforce in which the Aurum Institute participates. National engagement will be maintained through inviting National Department of Health officials to participate in the Project Steering Committee. In addition, we will make results available to the SANAC and other advisory bodies and government bodies.

1.5 Innovation

Our proposed implementation science research is to test three approaches to increasing timely entry-into-care: time-of-HCT point-of-care CD4 results to improve perception of health needs, a care facilitator to assist with

overcoming personal barriers, and transport assistance to overcome a structural barrier to care entry. Our approach is highly innovative because it:

- (1) Targets each major modifiable entry-into-care domain. This is important because excluding some domains may or may not identify a beneficial intervention; however, it precludes gaining insight in an optimal comprehensive entry-into-care system.
- (2) Will include the diverse geographic areas of urban, peri-urban, and rural in a single study, making the results highly generalizable.
- (3) Provides cost effectiveness analysis with comparison to the current situation thus having direct relevance to policy makers.
- (4) Models of the impact of the interventions on mortality and HIV transmission based on study parameters.

1.6 Study objectives

1.6.1 Primary objectives

- To compare the time to entering HIV care in each intervention arm against the standard of care arm over a 90 day period from study enrolment.

1.6.2 Secondary objectives

a) Intervention effectiveness

- To compare the proportion of participants in each arm entering care by 90 days from study enrolment.
- To compare the time to entering HIV care in each intervention arm against the standard of care over a 180 day period from study enrolment.
- Sup-group analyses. The primary endpoint will be re-assessed to evaluate for differences in response by the subgroups based on sex, geographical area (rural/urban), age group, presence of symptoms, and CD4 count.

b) Mortality

- To compare the time to mortality by 90 days from study entry by study arm.

c) Health Economics

- To compare the cost-effectiveness (comparative cost-effectiveness) for (i) each intervention against the standard of care, and (ii) the incremental cost-effectiveness of dual interventions versus the POC CD4 only intervention.
- To model the expected impact and cost per death (all-cause) averted and HIV transmission averted on all-cause mortality and HIV transmission using the empiric findings from each intervention arm and published data on the impact of cART on mortality and transmission.

1.6.3 Exploratory objectives

- To compare the proportion of cART-eligible patients who initiate cART within 90 days of study enrolment in each study arm.

2 STUDY DESIGN

2.1 Population and Setting

The implementation research study will be conducted in 2 districts – Ekurhuleni District (Gauteng Province) and Sekhukhune District (Limpopo Province). The study will be built onto existing Aurum HCT activities being conducted in these districts.

2.1.1 Description of geographical areas of study implementation

2.1.1.1 Ekurhuleni District

This is one of the 6 districts of Gauteng province of South Africa and the fourth largest Metropolitan municipality in South Africa. The district had an approximate population of 2.8 million people, accounting for 28% of the population in Gauteng and 5.6% of the national population (City of Ekurhuleni Annual Report 2010-2011). According to the 2001 Statistics South Africa Census report, Ekurhuleni has an almost similar distribution of males (50.74%) and females (49.26%). Black Africans are the dominant ethnic group (76.26%), followed by whites (19.44%). It is densely populated (1400 people/km²) compared to the whole of Gauteng (604 people/km²). The percentage of people living in poverty is 27% compared to 41% nationally. In the last HIV antenatal survey conducted in 2010, Ekurhuleni had the highest HIV prevalence in the province (34.0%) compared to other districts (Department of Health, 2010). The district reported a 250% increase in the number of HCT encounters from 170,576 in 2009 – 2010 to 683,923 in 2010-2011. It is unclear how many of these were positive and if they accessed pre-cART or cART care. At the end of the 2011 financial year, 86% of the 78 primary health care facilities, and all of the 7 community health clinics were providing cART (City of Ekurhuleni Annual Report 2010-2011).

2.1.1.2 Sekhukhune district

This is found in the northern part of South Africa and is one of the 5 districts in Limpopo Province. According to the district annual report for 2009-2010, the total population of the district is just above 1 million accounting for approximately 2.2% of the national population. Almost all (99%) of the population is comprised of Black Africans. The majority (94.7%) of the total population reside in the rural areas divided into 605 villages, while 5.3% reside in the urban areas of the district. About 33% of the population still depends on surface water. The economy is largely based on agriculture, mining,

and tourism. The district had the highest unemployment rate in Limpopo, at just above 60% compared to the national average of 49%. Females constitute the majority of the population at 55.2%, and account for 60% (vs. 42% national average) of heads of households since most males are compelled to seek work outside the district. The district has 81 public sector clinics and 7 hospitals. In the last HIV antenatal survey conducted in 2010, the district had an HIV prevalence of 16.6%, which was lower than the provincial average of 21.4% (Department of Health, 2010)

2.1.2 Rationale for selecting geographical areas of study implementation

The geographical areas of study implementation were selected for convenience and heterogeneity. Ekurhuleni and Sekhukhune districts are part of the 5 districts that Aurum has been tasked with the role of determining, planning, implementing, monitoring and evaluating changes in policies, guidelines, and professional practices within Department of Health Facilities. The overall aims of these activities are to strengthen the basic HIV care package within facilities, facilitate comprehensive community programs and collaborate with other partners working in the district. The experience of working in these districts, established platforms for community and stakeholder engagement, as well as knowledge of the referral networks in the districts present an advantage of implementing the study in these 2 areas.

The other principle reason for selecting these two districts is heterogeneity. As described above, Ekurhuleni is primarily urban and semi-urban with large in-migration and Sekhukhune is primarily rural with less in-migration. The geographical and socio-demographics heterogeneity will increase the generalizability of study findings and allow for subgroup analyses focusing on the effect of HCT delivery on entry-into-care.

2.1.3 The Aurum HCT Programme

Aurum provides HCT as a direct service to communities and in conjunction with the Department of Health as part of health systems strengthening in Ekurhuleni and Sekhukhune Districts. As part of health systems strengthening, HCT is used as a tool to engage with individuals at household level so that they receive comprehensive health assessments as part of the South African government's primary healthcare re-engineering strategy. Aurum currently delivers mobile HCT through the use of fully equipped mobile HCT vehicles, and this is completed by delivery of HCT at fixed sites where the Aurum offices are based in each district. Aurum has 4 mobile teams in each of the districts. These mobile teams are comprised of a team leader (enrolled nurse/professional nurse), 3 trained counselors including a counselor driver (with counseling skills encompassing adolescent issues). Each vehicle has 2 rooms in which counseling can be privately conducted. These mobile units target individuals at their work place, in public place (e.g. taxi ranks) or in residential areas. Mobile teams provide a significantly higher number of HCT than fixed site teams; therefore 1 counselor is tasked to man the fixed HCT site on a weekly rotation basis.

HCT is provided to all individuals according to the National HIV Counseling and Testing Policy Guidelines (2010). The first step is the provision of a pre-HIV test individual counseling session conducted which broadly discusses; assessment of individual risk, risk reduction, prevention strategies management options should the client test positive and TB screening. The client is then asked to provide verbal and written consent to (i) undergo HIV testing and (ii) to be contacted by Aurum staff for any form of follow up. Subsequent to this, the client is screened for HIV using the Abbott Determine HIV Rapid Test Kit. If the client is HIV positive, confirmation is done using the Trinity Biotech Uni-Gold Rapid HIV test. In the event of a discordant result between the 2 devices, a venous blood sample is collected and sent to an off-site lab for ELISA testing. After testing is complete both the counselor shows the test strip to the client and interprets the result. In post-HIV test counseling HIV negative testers are given comprehensive prevention information and encouraged to frequently test. HIV positive clients are counselled on possible emotional resources, and given information on how to reduce risk of HIV transmission, ongoing positive living, nutrition and healthy lifestyles. These clients are given referral letters and referred to health facilities of their choice that offer HIV care/treatment. Aurum HCT sites do not offer cART or pre-cART care packages.

2.2 Sampling

2.2.1 Screening of potential study participants for inclusion

- HCT at the study sites will be performed by routine HCT counselors who will work in close liaison with study staff. After routine counselors complete the HCT process, they will inform HIV positive clients about the study and refer consecutive willing clients to study staff.
- Study staff will welcome clients and give them information about the study and invite them to participate. During this information session, study staff will explain in lay terms the rationale of the study, study procedures, study risks and benefits and address issues of confidentiality.
- Clients willing to participate in the study will be screened using a standardized tool (Enrollment Form) to ensure that they satisfy inclusion criteria for study participation. Clients who fail to meet the inclusion criteria will be educated on the reasons for study exclusion and receive the standard of care to facilitate their linkage to onward care.
- Clients who are unable to complete enrolment procedures on the day of testing HIV positive, but are willing to participate in the study are still eligible to be enrolled within a 3 day period from the day of HIV diagnosis (in exceptional cases, this may be extended to 5 days where diagnosis is performed a day before commencement of the weekend). This enrolment window takes into consideration and gives an opportunity for clients who (i) are diagnosed in work places or other settings and have limited time for enrolment procedures, (ii) present for HCT with peers or partners and are not willing to undergo enrolment procedures out of fear of involuntary disclosure and (iii) clients who still need time to come to

terms with their diagnosis. Such clients will be reimbursed for their transport of coming back to the sites for enrolment (R50/USD6.7 Ekurhuleni District and R80/USD10.7 Sekhukhune District)

Table 2-1: Inclusion criteria for study enrolment

Participants will be included in the study if:

1. They are 18 years of age or older – at this age, individuals in South Africa can give consent for study participation without the need of a guardian. Additionally, these individuals are able to seek care independent of their guardians such that personal barriers affecting the individual and not the guardian can be specifically addressed.
2. They are able to provide informed consent for study participation
3. No prior self-reported registration at a health care facility for cART or any pre-ART care after an HIV positive diagnosis – this is particularly important because the primary endpoint of the study is entry into a healthcare facility for HIV care/treatment.

2.2.2 Soliciting informed consent for study participation

Participants who meet the inclusion criteria and are willing to participate will be asked to provide informed consent for study participation (see Appendix A).

- During the informed consent process, participants will be provided with a patient information sheet (PIS) that details the investigative team, purpose of the research, expectations from the client, risks and benefits of the study, protection of confidentiality and details of the local IRB.
- The study staff soliciting the informed consent will explain the details of the PIS to the client and offer the client the option to go through the PIS on their own. The client will be given an opportunity to ask questions and after this is done the study staff soliciting consent will ask the client to repeat in their own words what they understand about the study and what will happen to them if they take part.
- Because the client would have just received information on their HIV status and may find it difficult to synthesize the diagnosis and study related information, study information will be repeated to the participant once more one to two weeks later (at the time of the first follow up contact).
- In the event that the individual cannot read, the consent form will be read out to him/her by the person obtaining consent, again ensuring their understanding prior to obtaining written consent. If the individual is unable to read or write, witnessed oral consent or a thumbprint will be obtained after it has been ensured by the person consenting that the individual's consent is informed.
- Clients who agree to participate will be asked to sign the informed consent (IC) form (see Appendix A). They will be given copies of the PIS and IC forms. The original IC form will be filed in a lockable cabinet by study staff in a Source Documents File that contains documents with personal identifiers. Participation is voluntary, and those who refuse to participate will continue with the completion of referral letters and referral to the client's facility of choice for onward care. Such individuals (if willing) will be asked to explain the reasons for refusing to participate, these will be recorded and analysed by the investigative

team on an on-going basis. No prejudice or deprivation of the standard of care services will be placed upon individuals who refuse to participate in the study.

- At this stage individuals who refuse to participate will be identified as ‘screen-outs’ and those enrolled into the study as ‘participants’. Basic information of screen-outs will be kept including sex, age, and screening location. In addition a reason for non-participation will be sought. This will be used to determine the fraction of HCT clients eligible for the interventions who actually agree to receive the interventions and to assess for biases in selection and participation.

2.2.3 Collection of client locator information

- Locator information is comprised of participant details that can be used to identify the participant and are essential for successful contact and follow up of the participant. In brief, this includes:
 - participant names
 - phone numbers of participant
 - residential address
 - employment details
 - next of kin or designated individual contact details
 - phone numbers for next of kin or other designated individual
 - best time to contact participant
- The existence and functionality of cell phone contact numbers of the participant will be verified at the time of enrolment by calling the provided number with the participant present.
- Following provision of informed consent and collection of locator information, participants will be assigned a pre-generated unique study identification number.

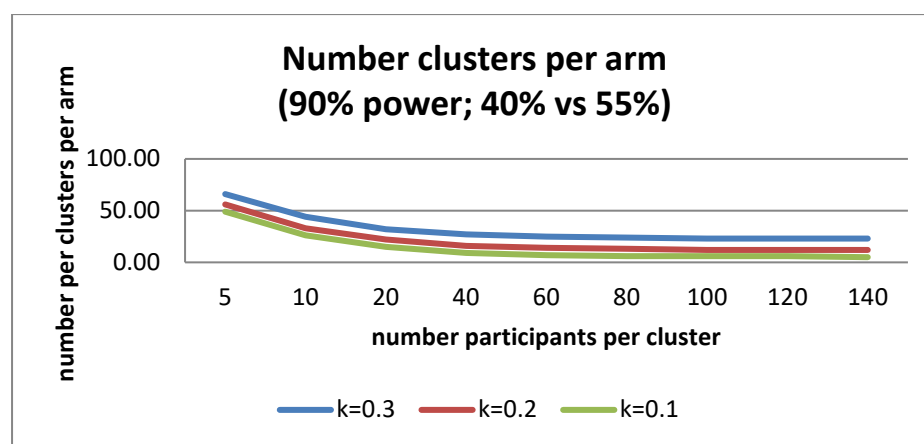
2.2.4 Randomization

2.2.5 Rationale for randomisation approach

- Individual randomization at the time of study enrollment immediately following HCT will provide a distribution of participants across study arms that is least likely to be subject to bias. Alternative randomization strategies could include recruiting all participants receiving HCT during a particular time frame (week or month) or at a particular HCT unit to a specific arm. The later would require a cluster-randomized design (CRT) where randomization is at the HCT unit level rather than the individual level. This technique is especially valuable for community-wide interventions which aim to capture both direct and indirect effects, though also used to reduce contamination in an individually randomized trial (Hayes & Moulton. 2009). There is a loss of statistical efficiency implicit in the CRT design due to correlations between observations on individuals within the same cluster, leading to larger sample sizes compared to

an individually randomized trial for same effect size. Therefore if an individual randomized trial design is suitable to answer the study question then that is preferred. For this study there may be some advantages for operating the intervention at the cluster level but it is not essential for it be delivered at that level. If we want to restrict the number of clusters per arm to say 6, (that is 6 HCT per arm), then with the coefficient of variation (k) of 0.1 (generally considered to be somewhat low) a sample size of 85 per cluster (total per arm 510) would be required for 90% power and comparing 40% versus 55% in the two arms (Figure 2-1). This compares to 244 per arm for an individually randomized study. Alternatively if we had 25 clusters per arm we would require 10 individuals per cluster (total per arm 260) for 90% power and comparing 40% versus 55% in the two arms. However a study with 25 clusters per arm would not be feasible with the budget or available HCT units (100 HCT units would be required). Even 24 (6 HCT units per arm) is beyond the available number of units and the budget of this study.

- We plan to be sensitive to issues of contamination from individual randomization and the potential for jealousy. Part of the participant information / informed consent process of this study will include explaining the different interventions and the random nature of who receives which intervention. We anticipate this to help with overcoming dissatisfaction or jealousy. In addition, we as most HCT clients will test HIV-negative, the total number recruited per day from any site will be on the order of 5 – 10 participants. We believe this will also help to reduce the risk of contamination. Finally, we will be including a qualitative component to assess participant experiences with the interventions. We will include discussion of knowing participants receiving other interventions in the Interview Guide to assess participant perceptions.



k= coefficient of variation¹

Figure 2.1: Analysis of cluster randomization approach

2.2.6 Summary of randomization procedures

- The stratified block randomization technique will be used to facilitate balance in allocation of participants to study arms. The statistician will sequentially allocate pre-generated participant numbers to a study arm

according to the block random assignment. This will be in the form of an opaque envelope showing the participant identification on top and the study arm assignment sealed inside.

- Based on the literature and our preliminary data, we anticipate differences in entry-into-care based on urban and rural residence and fixed versus mobile sites. Thus we will stratify randomization based on the study district (i.e. Ekurhuleni District -urban and Sekhukhune District -rural). We anticipate that through the randomization and the blocking processes, other important participant characteristics, such as gender and age, will be proportional between groups.
- After obtaining the locator information, the Research Assistant will retrieve the already prepared envelope that is labeled with the study identification number corresponding to that issued to the participant and use the information contained in the envelope to assign the participant to a study arm.
- After randomization, the participant will receive more detailed explanations on how the activities in the study arm he/she has been randomized to, will actually be operationalized. These explanations will also include the roles and responsibilities of the study staff and the participants in the delivery of interventions and contact information for care facilitators or transport facilitators, as appropriate. Study staff will provide participants with detailed information pamphlets on the four study arms that participants can take and read further at their homes.

2.3 Intervention I – Point of care CD4 testing

2.3.1 Goal of the intervention

The goal is to use point of care (POC) CD4 testing to help the participant, who may either be symptomatic or asymptomatic, to develop a more concrete understanding of his or her health status, a factor strongly associated with increased entry-into-care. The intervention will be implemented to target barriers in the domain of *health perception*. However, the effects of the intervention are not exclusive to health perception domains and they may also overlap in influencing the participant's self-efficacy to enter care.

2.3.2 Description of the test system

This intervention will utilize the PIMA™ CD4 test system. This is a test for the absolute enumeration of CD4 cells using small finger stick or whole blood samples and facilitates point of care (POC) testing in decentralized health settings. The test is comprised of a PIMA CD4 cartridge that contains dried reagents, a PIMA analyzer and a printer. The cartridge is a single-use disposable plastic device. The cartridge contains a plastic EDTA capillary tube that is used to collect the blood sample. The analyzer itself is a portable bench-top instrument (Size L 22cm X W 13cm X 16cm) that can be operated on external power or using on-board rechargeable battery. The CD4 results are displayed by the instrument in units of cells/ μ L and data can be retrieved and downloaded (onto a flash drive) by study staff at any time after the analysis.

2.3.3 Summary of procedures for POC CD4 intervention

Following successful randomization to one of the POC CD4 test arms, the following will happen:

1. Study staff will collect a low sample volume of 25 µL of capillary or venous blood for analysis on the PIMA analyzer.
2. The cartridge is capped and inserted into the analyzer for CD4 enumeration. On average, results will be made available within 20 minutes from insertion into the analyzer.
3. Once results are available, study staff will print 2 results. One will be issued to the participant and the other kept for study site records.
4. Participants will be given a copy of their results, which will be affixed to their referral letter, and they will be educated on the meaning of the CD4 results in relation to their health. Counseling will encompass: the role of CD4 cells in the body, an interpretation of the CD4 result in relation to immune-competency and eligibility for cART, and the importance of receiving further HIV care/treatment whether eligible for cART or not. Study staff will issue an information pamphlet summarizing the information discussed in the session. This session will only be performed once at the time of issuing POC CD4 results. Through increased disease state specific awareness we hypothesize that the participant will be more motivated to seek medical care.

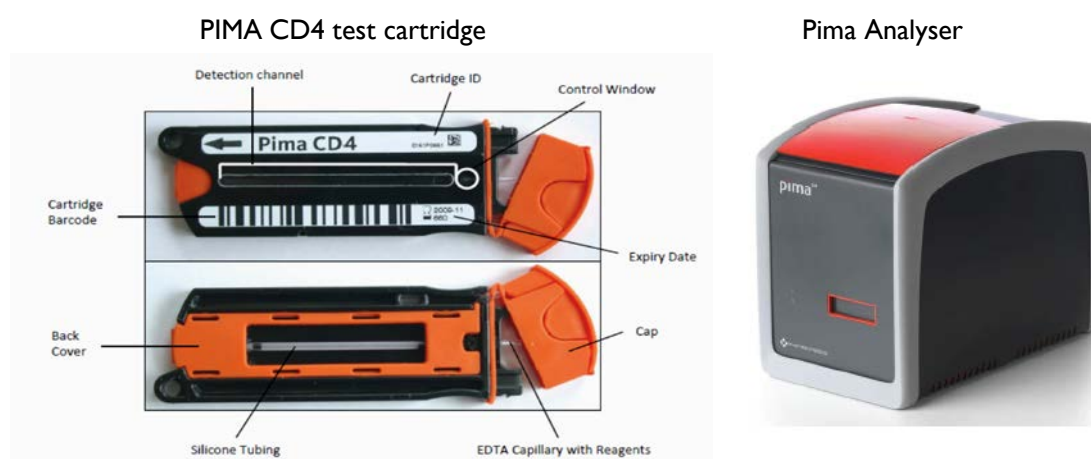


Figure 2.2: Pictorial presentation of PIMA POC CD4 testing machine and cartridges

2.4 Intervention II - Care facilitator/manager

2.4.1 Goal of the intervention

The goal of this intervention is to provide on-going counseling that is set to address an array of *personal barriers* that are interwoven and unique to individuals making them challenging to address during the relatively short pre-test and post-test counseling HCT sessions. When clinicians are asked what they perceive to be barriers to entry-into-care, the structural barriers of finances, transportation, or family care, are offered by over half of clinicians (Mayer 2011). A very different picture emerges when patients describe reasons;

personal barriers are paramount, with *fear* of people knowing their HIV status, *fear* of medication side effects, and *stigma* each reported by over 50% of participants in a South African study (Schneider *et al.* 2008). Findings from a qualitative study (unpublished Aurum data) in the proposed districts of study implementation have also revealed the existence of similar complexities faced by recently HIV diagnosed individuals.

In South Africa, on-going counseling has traditionally been provided to HIV infected individuals through support groups created in an ad hoc manner and often without a formal counseling structure. Benefits of these groups have been reported in empowering attendees to overcome personal barriers and attaining self-efficacy to cope with their diagnoses (Visser *et al.* 2005). While the benefits of group counseling cannot be discounted, evidence from literature (Kekana. 2011) and qualitative findings from Aurum HCT clients highlight gaps in this approach that can be potentially covered by an individualized counseling approach. Preliminary findings from a qualitative study (unpublished Aurum data) in the proposed districts of study implementation have suggests that clients have concerns about privacy and confidentiality in attending support groups and local community clinics where they are likely to meet people who know them. Other barriers to support group participation encompass issues around access, service and negative perceptions of support groups (Kekana. 2011).

The Department of Health through the Integrated Access to Care and Treatment (IACT) Programme is trying to strengthen the support group model (www.iactsupport.org/). However, caveats to the IACT model are that, (i) the major inward referral source of HIV positive clients is from clinic-based HCT or treatment programmes (i.e. clients accessing care at clinics), (ii) implementation in some districts has not commenced, (iii) the model is still susceptible to weaknesses in traditional group support models and (iv) no preliminary evaluation results on roll out and benefits have been published. However, if both the proposed intervention and IACT are found beneficial, we would suggest potential synergies can be established to support HIV clients diagnosed through community HCT programmes.

2.4.2 Description of care facilitation intervention

We have adapted a “strengths-based” time-limited structured care facilitation system for use in South Africa to assist in overcoming *personal barriers*. The foundation of the strengths-based system (see 1.1.4) is to assist the patient in identifying personal strengths and then applying these to problem solving (and is the basis of the ARTAS linkage to care program introduced in the United States). This applies to health care seeking behavior as it helps an individual to develop solutions to obstacles in the path to entering care including overcoming fears of stigma, disclosure, lack of self-confidence, and feelings of disempowerment. By using structured stepwise counseling techniques (using a combination of motivational interviewing techniques and strengths-based counseling) the intervention will be consistent across patients and will be reproducible in other settings.

2.4.3 Summary of care facilitation procedures

2.4.3.1 Duration of intervention

This is a time limited intervention with a maximum of 5 client sessions over a 90-day period.

Participants will also be transitioned out of the intervention upon successful entry into HIV care.

However, in some instances where there is a lack of community referral sources or the care facilitator adjudges the participant as requiring more critical psychosocial support to maintain self-efficacy; then additional sessions may be provided. One of the objectives of this implementation science research is to implement interventions as closely as they would happen in a real-life routine HCT programme.

We therefore believe that such outlier cases exist and it is the ethical responsibility of Care Facilitators to provide this additional support while maintaining both internal and external validity of the study.

2.4.3.2 Mode of contact

In-person contact will be considered as the first preference in conducting care facilitation sessions.

The investigative team has gained experience in using this approach through an on-going qualitative study requiring face to face in-depth interviews with recently diagnosed HIV positive clients. In the mentioned study, 80% of participants have successfully completed their face to face interviews, with the remainder failing to do so mainly because of time constraints or relocation to other geographical areas. In-person contact sessions can be conducted at Aurum office sites, public sector healthcare facilities, community halls or other public places where sessions can be conducted in a confidential and effective manner with minimal interference.

Telephonic contact will also be used in cases where face to face sessions are difficult to arrange. This gives the intervention flexibility in catering individuals with time constraints resulting from work, school or house duties. However, compared to the in-person contact the approach is susceptible to: losses of additional information from the client's non-verbal communication, discomfort in speaking on the phone for long periods, external interferences in the environment where client is receiving the call, and potentially prohibitive communication costs.

2.4.3.3 First contact between care facilitator and participant

Care facilitators will primarily be based at the Aurum site offices to conduct in-person and telephonic counseling sessions. In addition to this, the care facilitators will ensure that they keep lines of communication open with Research Assistants in the field so that they initiate the first contact with participants assigned to them at the time of enrolment.

Using a speaker phone the Research Assistant responsible for participant enrolment will telephonically contact the office-based care facilitator who will briefly introduce themselves to the and reiterate the general activities of the intervention to the participant.

If the participant has a cell phone the care facilitator will call the participants phone and ask the participant to save the number under a name that they can easily link to the care facilitator. Preferably during this call, the care facilitator and the participant will agree on the date and mode of contact for the first care facilitation session.

Participants will be informed that they will be reimbursed for travel expenses incurred towards case management sessions (R50/USD6.7 Ekurhuleni District and R80/USD10.7 Sekhukhune District).

Granted that the care facilitation will be provided in combination with POC CD4 testing, the above mentioned procedures can be conducted in the 20 minute period awaiting the completion of the POC CD4 test to avoid unnecessary waiting time.

2.4.4 Content of care facilitation sessions

1. The care facilitation sessions are client-driven. Therefore, the agenda, time and content will be adjusted to the client's needs (although the maximum number of sessions remains fixed). In the first session the care facilitator will:
 - (i) Re-introduce the goals of the intervention
 - (ii) Discuss concerns about the client's recent diagnosis
 - (iii) Commence identification of personal strengths, abilities and skills
 - (iv) Encourage entry into HIV care
 - (v) Discuss goals and activities to be implemented to enter HIV care
 - (vi) Provide information of relevant external resources (i.e. support groups, details of alternative HIV care providers, information on social grants, other HIV community based organisations)
 - (vii) Plan for the next session.
2. In the subsequent sessions, the care facilitator will continuously monitor progress and any issues arising from the previous sessions. The sessions will continue addressing the client's:
 - (i) Personal needs and barriers to linkage
 - (ii) Revision of goals and activities
 - (iii) Continuous encouragement to access HIV care.
3. As the number of sessions comes to an end or after the participant has successfully entered care, the care facilitator will commence transition planning. This involves:
 - (i) Emphasizing the time-limited nature of the intervention to the participant
 - (ii) Review past sessions with particular focus on identified strengths and goals that were set

- (iii) Review of community resources discussed during previous sessions and the important role of family support structures.
4. The intervention is designed to be holistic and tailor-made to help participants (where possible) to overcome their unique barriers in accessing HIV care. Additional practical support provided by the care facilitator will include (if requested and feasible): (i) escort to first healthcare visit to assist participants overcome the fear of health system navigation and, (ii) facilitated disclosure of participant's HIV status to friends or family.

2.4.5 Length of care facilitation sessions

Granted the client-driven of the intervention, the length of each individual session will be structured around the client's needs. However, the care facilitator has responsibility to modulate duration of the sessions and ensure that:

- (i) The sessions are focused on issues relevant to the goal of accessing HIV care.
- (ii) Sessions are not unnecessarily prolonged with minimal additional benefit to the development or review of the case plan.
- (iii) The participant is not fatigued or disengaging from the discussions (the point at which the session may be stopped).
- (iv) The cost of the sessions (i.e. telephonic sessions) do not resulting in unnecessary additional costs in conducting the sessions.

2.5 Intervention III -Transport assistance

2.5.1 Goal of the intervention

The goal of this intervention is to address one of the most frequently noted *structural barrier* to entry-into-care in resource constrained settings: prohibitive distance or transport cost to reach a health facility. In South Africa, the majority of patients accessing HIV care incur transport costs. These costs are higher in rural areas where the amount spent on transport is not only proportional to the travel distance, but the complexity of the transport network due to poor developed roads (Rosen *et al.*2007). In addition, findings from a recent qualitative study (unpublished Aurum data) have revealed that HIV positive individuals may be incurring more transport costs as a result of expressed preferences in seeking care from healthcare providers further away from their communities.

Although HIV care and treatment is provided for free in South Africa, direct costs for accessing care are significant and may account for more than 10% of the total household expenditure in 23% of households with a member on ART. In this study, 40% of ART service users in a rural site had to borrow money or sell assets to cope with healthcare costs, while other individuals were reliant on financial assistance from family, friends

and social networks to meet their costs (accessed at <http://www.health-e.org.za>). However, due to high rates of non-disclosure among recently diagnosed individuals, they may fail to receive financial assistance from support networks resulting in non-entry into care. These challenges exist within an environment where planned patient transport systems are not well established and the majority of patients use public buses and taxis to travel to health care sites.

We believe that ignoring a commonly cited barrier-to-care based on logistical challenges would lead to less impactful implementation science. If transport assistance does not help in the South African context, this would be an important finding as would a substantial increase in entry-into-care. From a government budget perspective, the relative cost effectiveness will need to be taken into account and will be determined as part of this project. The sustainability of this intervention is placed within the context of the ever increasing government expenditure on grants that are affected by mortality or morbidity due to delayed entry of HIV positive individuals into care. In particular, if this intervention is found to be beneficial it may have a positive impact in reducing expenditure on the Disability Grant for HIV positive individuals with CD4 counts $<200\text{cells}/\mu\text{L}$ (ZAR1200/month) and Foster Care Grants (ZAR770/month) resulting from HIV mortality (<http://www.sassa.gov.za>). In addition, it is plausible that we will identify subgroups that benefit substantially from this intervention. Identifying this need and an effective intervention will assist in evidence-based government health planning.

2.5.2 Summary of transport assistance procedures

2.5.3 Duration of the intervention

This is a time limited intervention with a maximum of 3 transport assists for healthcare visits over a 90-day period or until the client registers for HIV care with a healthcare provider, whichever comes first.

2.5.4 Disbursement of transport money

- The disbursement of funds to support the participant's costs will be initiated after a participant's self-reported healthcare visit. To reduce the levels of false reporting, study staff will emphasize the importance of ensuring that the participant claims transport support for actual visits made and encourage a working trust relationship with the participant. The study team will make efforts to ensure that the participants receive their allocated transport support within 24 hours of their reported healthcare visit. Where possible, the study staff will attempt to telephonically verify the participant's reported visit with the healthcare facility (i.e. patient's name and/or provided patient number). Participants reporting an unsuccessful healthcare visit will be asked to summarize reasons for non-completion of registration and plans of subsequent healthcare visits.

- Money will be disbursed to the participants with the option of direct transfer into bank accounts, in-person collection at Aurum site offices or electronic transfer through cell phones.

Collection from Aurum site offices

This method is also utilized by the SASSA for grant payments to recipients. We have adopted this for participants who have easy access to Aurum site offices in the project site districts and would prefer collection of the money in-person.

Electronic transfer of funds through cell phone technology

This option will cater for participants who do not have bank accounts, but have access to a cell phone. According to the recent census 89% of households have a cell phone making this option potentially applicable to a large proportion of participants. Money is transferred instantaneously via the participant's cell phone, with no additional downloads or extra kits required. Transfers are made using a unique withdrawal code that the participant can enter into an automated teller machine (ATM) or present to an accredited distribution agent (i.e. large or small scale retail shops) to get their money. According to the *Mobile Consumer in South Africa 2012 Report*, cell phone owners are increasingly embracing cell phone banking technologies, more so among the rural population.

2.5.5 Amount of transport support

- Few studies have quantitatively evaluated the transport costs incurred by HIV patients accessing HIV care services. One study assessing transport costs among patients accessing HIV care at 4 different sites (urban only), reported that participants spent a median of R20/USD2.7 to R30/USD4 per clinic visit (Kekana. 2011). Another study further showed that the top decile of the patients accessing care in urban and rural healthcare facilities spent R50/USD6.7 and R80/USD10.7 per clinic visit, respectively Rosen *et al.* 2007). These amounts are similar to those reported by Aurum HCT clients reporting to have accessed care. Additionally, in a previous study among 61 recently diagnosed HIV positive individuals, participants were reimbursed R50/USD6.7 and R80/USD10.7 to cover transport costs for study visits to Aurum site offices in Ekurhuleni and Sekhukhune districts, respectively. Participants reported that this was adequate in meeting their transport costs.
- A flat reimbursement for all participants depending on the project region (Sekhukhune-R80/ USD10.7 or Ekurhuleni-R50/USD6.7) will be implemented for standardization purposes facilitating reproducibility of the intervention and ease of implementation.
- Transport assistance will only be provided upon request from the participant and will not be initiated by study staff. However, patients will be sent weekly text messages as reminders of the availability of transport assistance but will need to contact study staff to receive transport re-imbursement.

2.6 Standard of Care

The role of this arm is to provide a baseline measure that can be used to assess the effectiveness of the combination interventions in improving the proportion of individuals entering care within 3 months. The

activities related to this arm have previously been described in 2.1.3 under the description of Aurum HCT. After successful randomization to this arm, study staff will ensure that participants have been provided with referral letters and that they have answered any questions that the participants have. The current standard of HCT includes neither, on-going counseling as part of care facilitation, transport assistance nor POC CD4 testing. Additionally, clients are not offered lab based CD4 testing either, they are advised to have these tests done at the referral facilities.

NB: It is important to mention that while basic elements of counseling (i.e. empathy and information dissemination) may overlap between basic pre-/post-test counseling under standard of care and care facilitation; the fundamental differences are that care facilitation sessions are (i) on-going (ii) purposefully structured to draw problem solving skills that can be applied to overcoming barriers, (iii) include additional components of disclosure counseling, and (iv) they are tailored to meet the requirements of the participant.

2.7 Study arms

We are proposing an open (non-masked) individually-randomized implementation science evaluation of the effectiveness and cost-effectiveness of combinations of three strategies to increase timely entry-into-care for HIV compared to the standard of care. For practical reasons to limit the number of study arms, we have selected to have two dual intervention arms to include both an intervention that occurs at a single time point (point-of-care CD4) and over time (care facilitator or transport assistance) and a single intervention arm limited to POC CD4. We believe this approach will add important new information for designing entry-into-care programmes and is achievable.

- Study Arm 1 - Standard of care
- Study Arm 2 - POC CD4 test
- Study Arm 3 - POC CD4 test and care facilitation/case management
- Study Arm 4 - POC CD4 test and transport assistance

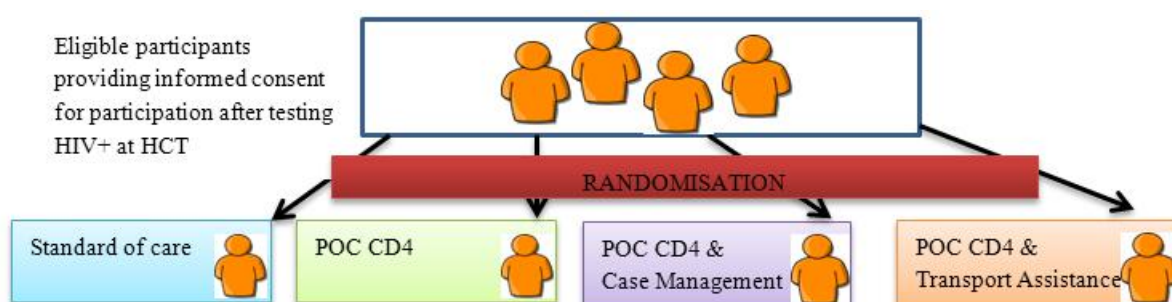


Figure 2.3: Schema of participant assignment to study arm

2.8 Follow up of participants

2.8.1 Follow up strategies

To ensure complete and accurate ascertainment of outcomes, we will use a combination of approaches. We have successfully used all three approaches in prior studies among HIV care recipients and believe they provide a robust approach to accurately ascertain participant entry-into-care status (Hoffmann et al. 2011; Dahab et al. 2010).

2.8.1.1 Telephonic follow up

- At the time of enrolment, study staff will collect the participant's telephone contact details (i.e. cell phone, landline and next of kin phone details). Participants will be asked to indicate the time at which they prefer to be contacted by study staff. Additionally, study staff will ask participants what they should say as way of introduction when they call the participant on their personal or next of kin's number (i.e. mentioning where we are calling from or what we are calling for). The purpose of this is to protect the participant's confidentiality, in the event that they have not disclosed their HCT encounter or HIV status.
- Once the recipient identifies him or herself as the participant, he or she will be asked to provide information to some of the following (where applicable) information to verify this: full name, date of birth, any research studies they have participated in or are currently participating in, the study arm they have been randomized to and what it involves, employment status, marital status. Once study staffs deem the responses to be satisfactory, they will continue with administration of the questionnaires and/or care facilitation sessions.
- Next of kin will be contacted in the event that study staff is unable to contact the participant after several unsuccessful attempts. In the event that the next of kin is contacted, study staff will introduce themselves as advised by the participant. The conversation will focus on soliciting information of the participant's whereabouts and how the study staff can contact the participant. In keeping with good clinical practice (GCP) guidelines, study staff will not divulge the participant's HCT information.

2.8.1.2 Auditing of HIV clinic records

- Clinic HIV care registers will be reviewed for verification of clinic utilization among participants who report health care visits at the time of follow up. At the time of enrolment, participants will be asked to provide consent for study staff to access their clinic records in order to verify health care visits and the understand the type of care they are provided with.
- Auditing of clinic records will be facilitated through the use of data abstraction forms. Data to be abstracted will include the information on the participant's: date of health care visit, details of care provided during visit, laboratory tests, medication supplies, cART preparatory visits (if applicable) and diagnoses of opportunistic infections.

- To implement these activities the study will utilize the network of Aurum Health Programmes teams that have regular contact with clinics in Sekhukhune and Ekurhuleni. The HCT units selected for this proposed project are based in catchment areas of these Aurum supported clinics. Thus Aurum has the relationships and capacity to achieve the needed clinic register verification. The actual register or clinical record review will be completed by clinic nursing staff or Aurum clinical mentors at the request of project staff, so as not to compromise confidentiality. Attempts will also be made to obtain this information from facilities that are outside the 2 project districts, including non-DoH healthcare sites.

2.8.1.3 Linkage to South African National Death Registry

- We will use national identification numbers to link with the Department of Home Affairs vital statistics register to identify deaths not otherwise ascertained by any of the follow up methods mentioned above.

2.9 Scheduling of follow up visits

This section outlines the follow up time points at which participants will be telephonically contacted by study staff to solicit information. These time points do not include the contact that is made with the participant specifically for care facilitation sessions and transport assistance.

Table 2-2: Follow up time points for contacting participants and activities involved

Visit #	Visit code	Time on study	Activities
1	0.10	0 days	Study enrolment and assignment to study arms
2	0.20	30 days	Verification of contact details – no interview
3	0.30	60 days	Verification of contact details – no interview
4	0.40	90 days	Follow up interview to ascertain entry into care
5	0.50	180 days	Follow up interview for participants failing to enter care within 90 days from enrolment

3 DATA COLLECTION AND MANAGEMENT

3.1 Instrumentation and measurements

3.1.1 HIV Rapid Testing

Principles of test

The diagnosis of participants for HIV at Aurum HCT sites is conducted by trained counselors and primarily relies on rapid HIV test kits, namely Determine ½™ and Unigold ½™. Both tests are based on an in-vitro visually-read immune-chromatographic assay for the qualitative detection of antibodies to HIV-1 and HIV-2 in human serum, plasma or whole blood. In both tests, a positive reaction is visualised by a pink/red band in the test region of the device. A negative reaction occurs in the absence of human immunoglobulin antibodies to HIV in the analysed specimen. Consequently no visually detectable band develops in the test region of the device. In the event that there is a discordant positive results, blood samples are sent to an off-site lab for ELISA testing. In such cases, results from the ELISA are considered as the confirmatory results. This testing protocol adheres to the DoH HIV testing guidelines and is associated with a very low rate of false negative (with the exception of very early acute HIV) and false positive test results.

Quality assurance

A quality control log is completed each day before the rapid HIV test kits are used. Procedural controls (negative and positive) are incorporated into each test strip and are labeled “CONTROL”. If the control bar does not turn red by assay completion, the test result is invalid and the sample should be re-tested. In addition to this, in every test it is expected that a red band should appear in the control window.

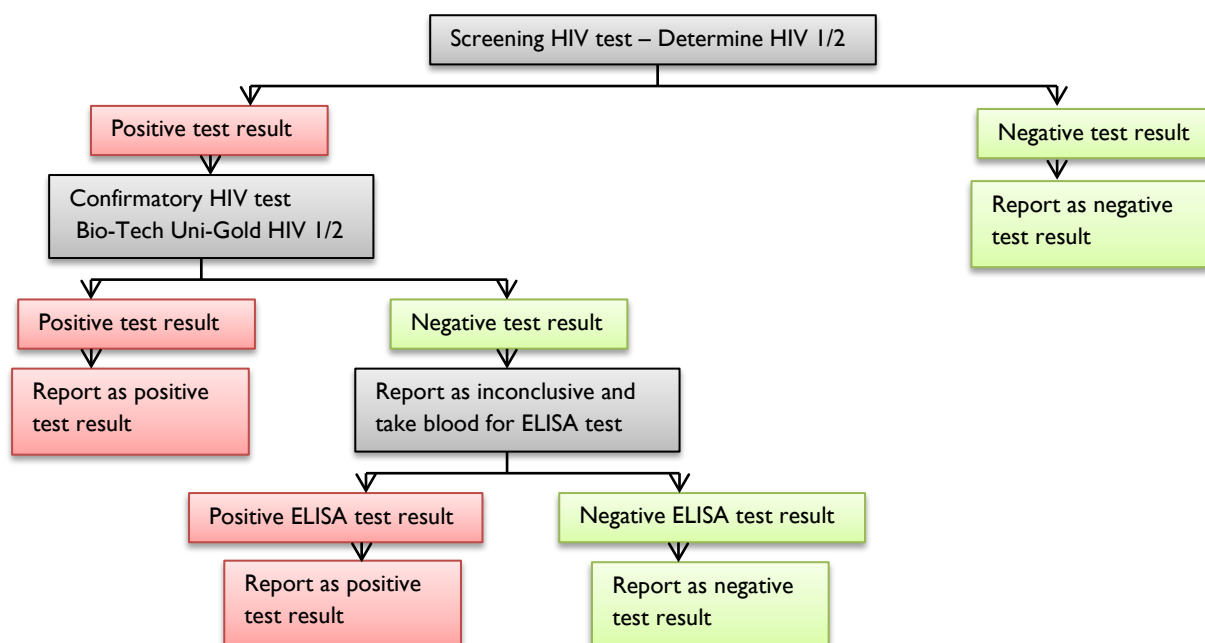


Figure 3.1: Algorithm for HIV testing

3.1.2 Point-of-care CD4 enumeration

Performance

The PIMA POC CD4 analyzer has previously been previously described in section 2.4.2. In terms of performance, the Pima CD4 test results from HIV-positive samples show a range between 0-1677 cells/ μ L with a coefficient of variation of 13.77%. For the HIV-negative samples the range is between 620-1992 cells/ μ L with a coefficient of variation of 10.1% (PIMA white paper).

Quality assurance

The instrument has built-in quality control features which include; (i) ejection of the test cartridge if the expiry date has been passed; (ii) error messages if there insufficient blood volume and (iii) error messages if stability of reagents falls out of standard limits. Additionally there are 2 ready to use 'normal' and 'low' control cartridges with a predetermined amount of immobilized fluorescent beads. Quality control logs will be kept to monitor the results issued by the PIMA Machine.

3.2 Data collection

Table 3-1: Measurement of primary endpoints

Endpoint	Unit	Definition	Source of information	Person collecting information
Time to entering HIV in each intervention arm compared to standard of care arm over a 90 day period from study enrolment.	Days	The number of days taken by participants to make their first HIV care visit to a healthcare provider in a 90 day follow up period from the time of study enrolment in each study arm	Self-report Participant CRFs Study Enrolment Log Clinic Data Abstraction forms	Research Assistant Care facilitators Health care staff at facilities

Table 3-2: Measurement of secondary endpoints

Endpoint	Unit	Definition	Source of information	Person collecting information
Proportion of participants entering HIV care within 90 days of study enrolment in each intervention arm compared to the standard of care arm.	Proportion (%)	Numerator: The number of participants with a first HIV care visit to a healthcare provider within 90 days from the time of study enrolment in each study arm Denominator: The total number of participants randomised into each study arm	Self-report Participant CRFs Study Enrolment Log Clinic Data Abstraction forms	Research Assistant Care facilitators Health care staff at facilities
Time to entering HIV care in each intervention arm compared to the standard of care over a 180 day period from study enrolment.	Proportion (%)	The number of days taken by participants to make their first HIV care visit to a healthcare provider in a 180 day follow up period from the time of study enrolment in each study arm	Self-report Participant CRFs Study Enrolment Log Clinic Data Abstraction forms	Research Assistant Care facilitators Health care staff at facilities
Time to mortality by 90 days from study entry by study arm	Days Mortality/100 person years of follow up	The numbers of days to mortality for participants in each arm over a 90 day period from the time of study enrolment	Participant CRF National Death Registry Reports from next of kin Home visits Clinic Data Abstraction forms	Research Assistant Care facilitators Health care staff at facilities
Costs of implementing each intervention	Rands (ZAR) , %	Absolute costs for implementing the interventions, comparative cost effectiveness of between interventions & standard of care, incremental cost effectiveness of dual interventions vs. POC CD4 only intervention.	Study financial records	Research Assistant Study coordinator Research Manager Management Accountant Health economist

Table 3-3 Measurement of exploratory endpoints

Endpoint	Unit	Definition	Source of information	Person collecting information
Proportion of cART-eligible patients who initiate cART within 90 days of study enrolment in each study arm	Proportion (%)	Numerator: The number of cART eligible participants initiated on cART within a 90 day period from the time of study enrolment in each arm Denominator: The total number of participants randomized into each study arm	Self-report Participant CRFs Study Enrolment Log Clinic Data Abstraction forms	Research Assistant Care facilitators Health care staff at facilities

3.2.1 Data collection tools

Table 3-4: Tools to collect participant information

Case Report Form	Purpose	Mode of tool
Informed Consent	A written record of the participant's informed consent to participate in the study	Paper form
Locator	Captures the personal and contact details of the participant	Electronic form
Screening, Eligibility and Enrolment	Enrolment of participants into the study	Electronic form
Baseline demographics	Captures information on the participants demographics at the time of enrolment	Electronic form
Demographics follow up	Captures information on changes in participants demographics after enrolment	Electronic form
Response to HIV Diagnosis	Captures information on HIV testing history and disclosure after diagnosis	Electronic form
Clinic visit	Capture information on participant healthcare visits	Electronic form
HIV/TB testing	Captures information on HIV/TB care received by the participant from health care provider	Electronic form
Case note abstraction	Captures information on participants healthcare information from clinic records	Paper form
Strengths assessment form	Used in care facilitation to assess participants' strengths	Paper form
Case plan form	Used in care facilitation to capture information on the agreed goals and activities to facilitate entry into care	Paper form
Off-study form	Used to document information on participants lost to follow up or withdrawing from the study	Paper form

3.2.2 Schedule of Case Report Forms

Table 3-5: Schedule of Case Report Forms

Case Report Form	Form Code	Visits:	Visit 1 Entry	Visit 2 (Telephone)	Visit 3 (Telephone)	Visit 4 (Telephone)	Visit 5 ¹ (Telephone)	Visit 6 (Telephone)
		Time On-Study:	0	30D	60D	90D	180D	180D after seeking care
		Visit Code:	01.0	02.0	03.0	04.0	05.0	06.0
Visit Contact Documentation	AD001		X	X	X	X	X	X
Screening, Eligibility & Enrolment	EL001		X					
Locator Form	AD004		X	[X]	[X]	[X]	[X]	[X]
Baseline Demographics	DM002		X					
Demographics Follow-Up	DM003					X	X	X
Clinic Visit	SS004					X	X	
HIV/TB Testing	SS005					X	X	X
Response to HIV	RK001					X		
Off Study	AD002			[X]	[X]	[X]	X	X
Case Note Abstraction ²	FV001					X	X	X
(Source Document) Case Plan	SS010		[X]	[X]	[X]	[X]	[X]	[X]
(Source Document) Strengths Assessment	SS011		[X]	[X]	[X]	[X]	[X]	[X]

X required CRF, [X] may be required if updated or as necessary

¹ Visit 5 only occurs if participant had not entered into care at visit 4 (90D).

² Date of Case Note Abstraction will differ from date of visit. This CRF is only completed twice dependent on trajectory of follow-up.

Table 3-6: Administrative data collection tools

Name of tool	Purpose	Mode of tool
Study enrolment log	Captures information on consecutive clients enrolled into the study	Paper form
Study number issue log	Reference source for issuing study numbers to enrolled participants	Paper form
Travel reimbursement log	Captures information on amounts reimbursed to participants for face to face sessions with care facilitators subsequent to the day of enrolment	Paper form
Transport assistance log	Captures information on amounts reimbursed to participants as part of the transport assistance intervention	Paper form
Call log	Captures information on the telephonic attempts made to participants for study purposes	Electronic form
POC CD4 log	Captures information on the POC CD4 tests performed by the site	Paper form
Quality Control log	Captures information for required quality control procedures for HIV testing and POC CD4 testing	Paper form
Case notes	Used in care facilitation sessions to capture details of discussions with participants	Paper form
Costing log	Used to record all service delivery costs for use in costing	Electronic form

3.3 Database management

3.3.1 Structure of the database

All participant data will be inputted into a SQL-based server database by research assistants at the study sites or entered from paper-based CRFs by trained data capturers at the study sites. The database will be designed in a format that allows entry of data offline and pooling off the data onto the Aurum main server when the device is connected onto an internet line; this allows flexibility of real-time data collection without the risk of losing participant information. All paper study records (e.g. consent forms, screening logs) will be kept in a secure location accessible only to authorised study staff, investigators, and monitors. For mobile HCT units, the files will be kept at the Aurum Ekurhuleni Offices or the Burgersfort Regional Office (Sekhukhune)

3.3.2 Access to the database

Access to the database (data entry, reporting, and extraction) is controlled by the Data Manager. Study personnel requiring access to the database must complete required documentation and training prior to receiving the necessary username and password.

3.3.3 Data entry validation

Electronic CRFs are programmed with entry validation checks to ensure data entered complies with the expectation for that variable. All entry checks are listed in the database specifications (data dictionary) provided by the Software Project Manager at the time of database sign-off. Post data entry checks are compiled in the form of SQL or STATA™ 11 command lines by the Data Manager over the duration of the study as data review and cleaning procedures. These types of checks may be requested by the study staff. Post-data entry checks are run on a bi-weekly basis and always prior to a monitoring visit. The DM provides a list of these queries to the monitor for review and resolution at the study site.

3.3.4 Locking of final database

The final study database is locked to changes after the clean file form has been signed. Final storage of the database is with the production folder structure together with all the Metadata, source data and the user written programs and the version of the system used to produce the database. The folder is given a special icon to show it is locked and the available choices are restricted to reading the data.

4 STATISTICAL CONSIDERATIONS

4.1 Sample size

- Our primary objective is to compare each intervention strategy to the current standard of care. Thus we propose to power our study to assess for an operationally relevant difference in HIV care entry within 90 days of testing HIV positive at HCT. Data from several sites in South Africa as well as other African programs suggest that approximately 30-60% of HCT patients enter into care within 3-6 months of testing HIV positive. We have chosen to use 40% as our estimate of the expected proportion entering care within 90 days under the current standard of care, as the studies representative of decentralized HCT programs have reported a 30-40% risk of entry into HIV care. We have taken as operationally meaningful an increase in entry-into-care of at least 15% based on a minimum effect needed to make an intervention appropriate from a policy perspective.
- The conservative approach to sample size calculation is to adjust for multiple comparisons is to assume a type I error of $5\% \div \text{number of comparisons}$ (Bonferroni correction). With four arms, three of which involve interventions we have proposed 3 comparisons as part of the primary outcome (SOC vs. dual intervention 1, SOC vs. dual intervention 2, SOC vs. POC CD4 only; note this does not include comparing the two dual intervention arms), thus a conservative alpha is 0.017 (0.05/3).
- For a 15% difference between study arms and taking into account multiple comparisons there is at least 99% power with 625 patients per arm. Assuming 10% loss to follow up and 560 evaluable participants, then for a 15% difference by intervention arm, taking into account multiple comparisons the study will still possess at least 99% power
- Therefore we propose a sample size of **625 participants per arm** for a total of **2500 participants**.
- Under the same scenario for the secondary objective comparing dual interventions vs. the POC CD4 only intervention assuming at least a 10% difference, the study power is 77-81%, taking into account multiple comparisons.

Table 4-1: Power based on a type I error of 5% and 560 evaluable patients

Control	Intervention	Power ¹	Power ²
30%	45%	>99%	>99%
40%	55%	>99%	>99%
50%	65%	>99%	>99%
Single intervention	Dual intervention	Power ¹	Power ²
30%	40%	93%	81%
40%	50%	91%	77%
50%	60%	91%	77%
60%	70%	93%	81%

¹ no adjustment for multiple comparisons

² conservative approach to adjustment for multiple comparisons (alpha/5=0.01 rather than 0.05)

4.2 Quantitative data analysis

Quantitative data analyses will be performed using STATA™ (STATA Corporation, College Station, TX). Analyses will use methods appropriate for individually-randomized trial design. CONSORT (2010) guidelines will be used for the reporting of this trial. The four study arms are as follows:

1. Standard of care
2. Point of care (POC) CD4 alone
3. POC CD4 with transport to the clinic for treatment
4. POC CD4 with care facilitation

The primary and secondary outcomes will be based on three pairwise comparisons of each intervention arm with the standard of care arm. Analysis of the primary outcome will also include two pairwise comparisons of each dual intervention arm versus the POC CD4 alone. All analyses will be based on intent to treat, defined as including all randomised participants in the arm they were randomised to, regardless of what was actually received. Hypotheses tests for analyses of each intervention arm versus standard of care for the primary and secondary outcomes will be conducted with a Bonferroni correction to take into account multiple comparisons. This will result in all hypothesis tests being based in 0.017 (0.05/3) significance level. During analysis the analytic team will be blinded to intervention arm (coding will be used for the four arms).

Information on deaths and date of deaths may come from multiple sources and therefore a data hierarchy will be used to define the date of death for participants. Data sources include: (i) Home Affairs database, (ii) clinic, (iii) participants contacts (as listed on locator form). Dates of death from these sources may be estimated. If death dates from multiple sources all fall within 2 weeks of each other, then the earliest of non-estimated dates of death will be used, otherwise the earliest of all the dates will be used. If there are discrepancies between dates of greater than 2 weeks then data will be reviewed, masked to study arm, by a sub-set of the investigators in order define the date of death.

4.2.1 Baseline characteristic comparison by intervention arm

Baseline characteristics will be described by study arm and part of a Table 1 of the primary analysis. Quantitative variables will be summarised by mean and standard deviation or median and inter-quartile range, depending on whether data are normally distributed or not, respectively. Categorical variables will be summarised as frequencies and percentages.

4.2.2 Study flow

A participant flow diagram will be generated with the drop off of participants from the time of recruitment to outcome determination, by intervention arm. (Figure 1 of a manuscript). This flow diagram will include losses to follow-up, deaths, entry-into-care, and under observation but not yet in care.

4.2.3 Primary endpoint

4.2.3.1 Time to entering HIV care within 90 days from study enrolment

“Entering care” is defined as: documented evidence from clinic records of attending a health facility for HIV care visit for non-acute HIV care (opening an ART file/pre-ART file or in ART/pre-ART register). Time to entering care within 90 days of study enrolment is defined as time from randomization to earliest of (i) first visit to a health facility for HIV care (based on definition above) ; (ii) death; (iii) 90days from randomization. The event of interest will be first visit to a health facility for HIV care. Time to entering care will be summarised using Kaplan-Meier curves by intervention arm (Figure 2 of a manuscript). The log-rank test will be used to compare survival curves. In addition, the hazard ratio for time to entering HIV care for each intervention arm versus standard of care will be calculated along with its associated 95% confidence interval (CI), using Cox proportional hazards regression. The p-value will be based on the likelihood ratio test and adjusted using a Bonferroni correction (see 4.2). Cox proportional hazards regression will also be used for the adjusted analysis if imbalance at baseline is noted.

The following stratified (sub-group) analyses for the primary outcome will be conducted: sex, rural-peri-urban, age group (two strata), presence of symptoms, and CD4 count groups (two strata). These categories have been selected due to theoretical or reported for differential response to interventions. For example, men and women may face different personal barriers and benefit differing amounts for each intervention. Rural participants may benefit more from assistance with reaching a clinic while this may not markedly increase entry-into-care by peri-urban dwellers. Similarly, symptoms or lower CD4 count may pre-dispose individuals to respond to interventions and enter-into-care. Identifying differences in intervention effect by subgroup is important to (1) identify target populations for a national implementation of a strategy and (2) provide further insight into success or failure of an intervention to improve timely entry-into-care in the primary analysis. The intervention effect will be calculated for each strata using Cox proportional hazards regression and a p-value for interaction calculated using the likelihood ratio test.

4.2.4 Secondary endpoints

4.2.4.1 Proportion entering care by 90 days from study enrolment

This outcome is defined as the number of participants in care by 90 days divided by the number of participants randomized. This is similar to the primary endpoint, differing only that it is a proportion entering care rather than a time to entry-into-care analysis. We believe it is important to do for comparability with any analyses that only provide proportions entering care. The difference in and

ratio of proportions by study arm and associated 95% CI will be calculated and P-value based on Pearson's chi square test with Bonferroni correction. If any imbalance at baseline is observed then an adjusted risk ratio will be calculated using binomial regression.

4.2.4.2 Time to entering HIV care within 180 days from study enrolment

Time to entering care within 180 days of study enrolment is defined as time from randomization to earliest of (i) first visit to a health facility for HIV care (based on definition in 1.2.2) ; (ii) death; (iii) 180days from randomization. The event of interest will be first visit to a health facility for HIV care. Analysis will be conducted using the same methods as for the primary endpoint.

4.2.4.3 Mortality by 90 days from study enrolment

Time to death is defined as time from randomization to earliest of (i) death; (iii) 90days from randomization. The event of interest will be death. Analysis will be conducted using the same methods as for the primary endpoint.

4.2.4.4 Modelling mortality & HIV transmission

To model the expected impact and cost per death (all-cause) averted and HIV transmission averted on all-cause mortality and HIV transmission using the empiric findings from each intervention arm and published data on the impact of cART on mortality and transmission (see section 4.2.7 below).

4.2.4.5 Health Economics

To compare the cost-effectiveness (comparative cost-effectiveness) for (i) each intervention against the standard of care, and (ii) the incremental cost-effectiveness of dual interventions versus the POC CD4 only intervention (see section 4.2.6 below).

4.2.5 Exploratory endpoint

4.2.5.1 Initiation of cART among those eligible

For this outcome analysis will be restricted to study participants with a CD4 count <350 at enrolment, based on the POC CD4 data for the intervention arms and the laboratory-based flow cytometry test for standard of care participants. Time at risk will be measured from enrolment into the study to the earliest of (i) initiating cART; (ii) death, or (iii) 90days from enrolment. Analysis will be conducted using the same methods as for the primary endpoint.

4.2.6 Cost effectiveness analyses

We will calculate strategy-specific and total health system costs (strategy and downstream) for each intervention. In calculating costs, we will include the variance estimates from the direct costs from each strategy and perform sensitivity analyses around strategy-specific costs. Capital equipment will be depreciated 3% annually. In addition, we will perform sensitivity analyses around the potentially less precise downstream health costs. Individual data will be incorporated into a multi-level linear regression model to estimate the incremental net increase in entry-into-care, mortality, and estimated health benefit. Using the linear regression approach we will be able to account for correlations between costs and effectiveness at the individual level. We will use these results to estimate the incremental cost-effectiveness ratio (ICER) and will conduct extensive one-way and multi-way sensitivity analyses to describe the parameters that are most relevant to considerations of cost-effectiveness, and probabilistic uncertainty analysis to describe the overall model variability associated with uncertain parameter estimates.

4.2.7 Impact modeling

We will use a Markov state transition model to represent the processes and outcomes experienced by patients testing HIV positive to estimate the effects on (1) mortality and (2) HIV transmission by each strategy compared to the standard of care. The model will include variables of CD4 count at HIV diagnosis, time to entry-into-care, time to ART initiation, entry-into-care intervention, mortality by CD4 count at HCT and delays, HIV transmission risk by HIV RNA and age, and costing for each pathway. The model will be parameterized from study data when available - proportions entering care, starting cART, and having illness outcomes (e.g. hospitalizations, acute clinic visits, deaths) - and from the literature when not available from the study data (e.g. the longer term effects of cART initiation versus delay, HIV transmission). The reference scenario will be the standard of care strategy. We will perform extensive one-way and multi-way sensitivity analyses on all model parameters. To assess the impact of simultaneous changes in all model parameters, we will perform multivariate uncertainty analyses, varying all parameter estimates over beta distributions (for variables bounded between 0 and 1) or gamma distributions (for variables bounded between 0 and ∞), with means set to expected parameter values and standard deviations based on the variance observed in study data (for parameters obtained from the study) or as reported in the literature.

5 PARTICIPANTS' PERCEPTIONS OF BARRIERS AND FACILITATORS TO CARE AND TREATMENT

5.1 Objectives

To explore the barriers and facilitators of seeking HIV care and starting cART, by study arm at 90 and 180 days from the time of study enrolment

5.2 Design

We will conduct a sub-study of barriers and facilitators of seeking care. The study will be conducted in two parts. Firstly, we will conduct two cross sectional semi-structured quantitative questionnaire surveys, one at the 90 day follow up visit and the second at the 180 day follow-up visit. The surveys will be conducted with all participants who reported that they did not seek care and/or treatment at either visit. This is with the aim to quantify reasons for attrition from care and/or treatment. Secondly, at 180 days post enrolment we will conduct a qualitative study using in-depth interviews with a random sample of participants randomized in each arm of the study. Our aim will be to explore participants' perceptions of what factors, if any, helped or hindered their ability to seek care and to start cART.

5.3 Sampling

The cross sectional surveys will be conducted with: (i) all participants who report not seeking care or (ii) those who report seeking care but not starting treatment.

The qualitative interviews will be conducted with a random sample of participants pre-selected systematically using a full listing of enrolled participants identification numbers. Prior to systematic sampling the list will be stratified by randomization arm to ensure appropriate representation from each arm of the study. We aim to select approximately 10% of participants in each study arm. This will be approximately 60 persons in each arm. We believe that this number, after accounting for non-responders, will give us a sample size that will enable us to reach content saturation, as well as being logistically feasible to interview. Once the participant identification numbers are selected, the study file associated with those numbers will be marked as selected for the qualitative study.

5.4 Study procedures

Each participant reaching the 90 day visit will be assessed for the primary study outcome of whether they attended HIV clinic and secondly if whether they started cART. Every participant who reports not seeking care or seeking care but not starting treatment will be interviewed using the semi-structured quantitative questionnaire instrument. The interview guide will direct the research assistant to a general discussion of

barriers to or reasons for entry-into-care. In addition, the guide will steer discussions on the perceived benefits of the received interventions and of barriers that were not addressed in the intervention they received. For example, participants not in the transport arm will be probed regarding transport issues. The study guide will also include recommended starting points for a discussion of contamination from other study arms on the participant's attitudes. A repeat interview will occur at the 180 day visit.

Once the participant selected for the qualitative interviews reaches the 180 day follow-up visit, s/he will be asked again if they are still willing to take part in an in-depth qualitative interview. The interview can be conducted on the same day or at a later day (preferably within one week of the follow-up visit) if that is more convenient to the participant. The participant will be asked if they prefer to conduct the interview in person or telephonically. If in person, the costs of coming to the research office will be reimbursed on the interview day. All interviews whether telephonic or face to face will be recorded and transcribed verbatim.

5.5 Data Analysis

Qualitative interviews, whether face to face or telephonic, will be transcribed verbatim and then translated into English. All transcripts will be perused on a line-by-line basis and codes will be developed to label key themes in the data and to develop a coding scheme. We will then analyze the content of each script using the coding scheme to identify the most common or recurrent themes. A mixed method approach using triangulation of qualitative and quantitative data will also be performed to better understand the effect of each strategy on barriers to the strategy success with a key a priori focus on assessing the importance of multiple interventions for entry. We will use NVivo software to map themes across transcripts. Descriptive data analysis of survey data will be performed using Stata software (Stata Corp., College Station, Texas, USA).

Interviews will be reviewed and coded in an on-going manner to allow for adjustments in the interview guide and to assess whether thematic saturation has been reached and further interviews are unnecessary for the given intervention arm.

6 STUDY LIMITATIONS

a) Participant follow-up may increase entry-into-care for all arms, including the standard of care arm.

We believe that it is a reasonable trade-off to obtain accurate ascertainment of status. In addition, the magnitude of the difference in entry-into-care is our focus rather than describing the situation with the current standard of care. The close follow-up in each arm will help to overcome the limitation of several prior studies that evaluated entry-into-care based on presenting to a single study-affiliated clinic, and that were unable to account for participants who attended clinics elsewhere or died prior to clinic attendance.

b) Lack of targeted interventions for mental illness or alcohol and substance abuse

There is little work from Africa describing the effect of these issues on HIV testing or uptake of care, making designing a targeted intervention challenging. However, we believe that the flexibility of the strengths-based care facilitation approach will allow identification of mental health and substance abuse barriers to entry-into-care and help with problem solving. If we identify mental illness or substance abuse as important factors associated with delayed entry-into-care, this will be an important finding and an area for further implementation research and the development of dedicated programs. Targeted interventions require information on mental health and entry-into-care and ART initiation. We anticipate forthcoming results from observational studies to be useful for future operational research.

c) Single domain arm and dual combinations of combined domain strategies without a triple intervention arm

Our hypothesis is that multiple domains must be overcome to achieve high levels of entry-into-care. However, by only using combined arms, we would not be able to directly determine the effect size of a single intervention. However, we believe the use of multiple arms with each intervention assessed in at least two arms will allow us to estimate and model the relative benefits of the three interventions.

d) The primary benefit of HIV care is derived from cART while our primary outcome is clinic entry.

Delays in cART initiation may occur as a result of multiple factors such as delayed entry-into-care, HIV staging, evaluations for TB, the quality of service delivery in a clinic, and possible cART drug stock-outs. By focusing on the patient-level aspects of entry-into-care following HIV diagnosis, we will address the least understood and least intervened upon point in the HIV diagnosis and treatment cascade.

e) The period of 90 days is arbitrary.

90 days is a commonly used cut-off for entry-into-care studies, however, little work has been done on the optimal timing. This study will provide an opportunity to do just that through assessing outcomes by time-to-HIV care entry. Through this we hope to propose an optimal target for getting HCT clients into care following testing HIV positive.

7 ETHICAL CONSIDERATIONS

7.1 Regulatory approvals

This study will be conducted according to Good Clinical Practice (GCP) guidelines and completed in compliance with international and local human subject research guidelines. Prior to participant recruitment, ethical approval will have been sought and obtained from the Sekhukhune DoH Ethics Board, Ekurhuleni DoH Ethics Board, the University of the Witwatersrand Human Research Ethics Committee, the Johns Hopkins University IRB, and the London School of Hygiene and Tropical Medicine Ethics Committee.

7.2 Risks and benefits

This implementation research places participants at minimal risk and may provide benefit if it is successful in increasing entry-into-care for HIV. The greatest risk to the participants is a breach of confidentiality regarding HIV status or incarceration history; this risk will be minimized by (1) secure storage with limited access to all documents, (2) use of unique study identifiers on all study forms, and (3) use of discreet language that does not refer to HIV diagnoses by care facilitators and tracers when speaking with the participants either telephonically or in person. Phlebotomy procedures may cause discomfort to the participants, but these procedures will be performed by professionally trained staff. Study recruitment will occur following testing HIV positive. This is often a distressing time for a potential participant. However, for the study to effectively assess entry-into-care strategies, recruitment must occur at that time point. We propose to review the participant information sheet during the study contact subsequent to enrolment to assure understanding of the study and desire to continue to participate.

7.3 Batched CD4 testing

In order to assess secondary endpoints (for the standard of care arm) and to inform the state transition model, CD4 count values will be needed. We propose batched retrospective testing as real-time testing may influence study outcomes. CD4 testing will be done for all participants in the standard of care arm and 10% of participants in the intervention arms. Although we will be performing batched CD4 testing, when results are available they will be communicated to participants and a clinic of the participant's choice.

7.4 Participant consent

Informed consent will be sought from potential participants using information sheets available in relevant languages (i.e. Sesotho, isiXhosa, isiZulu, Setswana, Xitsonga, Afrikaans, and English). Written informed consent will be sought, with the assistance of a translator where necessary, using standard consent forms. Participants unable to read or write will be asked to make a mark or thumbprint in the presence of a witness.

7.5 Psychological stress

The period following an HIV diagnosis can be stressful. As part of the South African National HIV Counseling and Testing Policy Guidelines, psychological counseling will be provided by trained counselors to all clients undergoing HCT during pre-test and post-test counseling. During the study we will ensure that a counselor who is trained and experienced in HIV counseling will conduct the interviews and provide counseling if and when required during the interviews. Once the counselor makes a professional assessment to the effect that the participant is becoming emotionally unstable or upset, they will stop the interview and ask

the client on how they are coping with the interview, if they are still willing to continue or would prefer to avoid certain questions. Participants requiring additional intensive psychological support will be referred to counselors/psychologists at a clinic to which they are referred.

7.6 Confidentiality

All study records will be managed in a secure and confidential fashion. All records will be stored at the study sites and Aurum Head Office in locked filing cabinets and access to the records will be restricted to specified study team members. Case report forms and care facilitation documents will be identified using the participant's study number only, with locator information stored separately. Participants in the transport assistance arm will not travel with other participants to the health facilities without providing prior consent.

7.7 Participant withdrawal

Participants may voluntarily withdraw from the study for any reason at any time after counseling with study team. Participants may also be withdrawn if the study sponsors, or other national regulatory authorities, or any of the Institutional Review Boards (IRB) terminate the study prior to its planned end date. Every reasonable effort will be made to complete a final evaluation of participants who withdraw from the study. Study staff will record the reason(s) for all withdrawals in participants' study records.

7.8 Disbursement of monetary funds

Participants attending care facilitation sessions in-person will have their transport costs reimbursed for each session visit at a standard fee of R50/USD6.7 and R80/USD10.7 for Ekurhuleni and Sekhukhune participants, respectively. Participants assigned to the transport support arm will also receive the same amounts to subsidize their transport costs for each HIV healthcare visit. To monitor change of contact details and encourage communication with the study staff, participants will receive airtime valued at R15/USD2 on Day 0, 30, 60, 90 and 180. Previous Aurum studies have had similar strategies approved as non-coercive and these strategies have been reported to be effective towards the retention of participants within studies making telephonic follow up easier to conduct.

7.9 Dissemination and reporting of results

The investigative team will undertake the duty, in consultation with the sponsor and South African Government, to disseminate study findings in an appropriate and timely manner. The team will disseminate information considering the sensitivity of the funding, suitability of the audience and appropriateness of the communication strategy. The primary targets of dissemination is the Government of South Africa, HIV care

organizations in South Africa and elsewhere in Africa, health policy makers in South Africa and the rest of Africa, and the funder. The investigative team will communicate directly with the Government of South Africa and the funder. In addition, the investigative team will use the skills of the Aurum Marketing Department for further dissemination of findings and will submit materials to conferences and journals for wider dissemination. The department has also synthesized and rewritten study findings making them understandable and usable for general audience. Below we describe the dissemination considerations for different target audiences.

a) Study funders (USAID)

The team will disseminate study findings to the funder through the use of progress reports and a final report. The purpose of this is to ensure that the funder is able to monitor the study progress and evaluate the final project deliverables against the objectives that were set out to be achieved in the agreement. Selected team members will also be expected to attend the annual investigator's conference in Washington, DC. These activities will be carried out throughout the project lifecycle and post-study close out.

b) Study participants

Study participants will be asked if they are willing to be informed about the findings from the research study. Study participants will be informed in simplified language; how many people participated, general perceptions of the interventions by other participants, evaluated impact of the interventions and the way forward. Various channels will be explored to do this, including; telephone, email, sms, snail mail, newsletters, brochures, Aurum website. . These activities will be carried out within a year of production of final study report.

c) Thol'impilo Project staff and Aurum Health Programmes

Information will be continuously disseminated to the internal Thol'impilo project staff and the Aurum Health programmes staff through the use of status reports and the Aurum website. The purpose of this is to shape the future agenda and approach of Aurum to the delivery of community HCT. These activities will be carried out throughout the project lifecycle and post-study close out.

d) Department of health, policy makers, health advocacy groups

The team will disseminate results to the DoH, policy makers and other government bodies that include: District, Provincial, and National South African Department of Health as well as indirect stakeholders involved in policy and advocacy including the South African National AIDS Council (SANAC), the Southern African HIV Clinicians Society, Treatment Action Campaign, UNAIDS, and the WHO. . Furthermore, two of the investigators on this study (Prof. Gavin Churchyard and Dr. Salome Charalambous) sit on the SANAC as advisors to the Government of South Africa. In addition, Aurum staff provide program and research updates at regular Provincial "Partner" meetings in Gauteng and Limpopo Provinces (the settings for the proposed project) which occur approximately 6 times a year. All relevant Aurum projects are discussed at these meetings to inform Provincial Government and to receive input from Provincial Government.

Additionally, in larger projects, such as the proposed project, Aurum assembles a project steering committee to facilitate discussion among policy and research leaders in the field to discuss the project and provide input. These meetings occur prior to launch and annually thereafter. We have invited Dr. Thobile Mbengashe the National Department of Health (and propose to invite individuals from the pre-ART and entry-into-care focal points), Dr. Alistair Reed of UNAIDS, and Dr. Francois Venter of the Southern African HIV Clinicians Society to join. We will invite Paul Mafokeng of the DoH and also wish to include relevant USAID team members. The team will use; the final study reports, policy briefs, annual stakeholders meetings, community advisory board meetings, partner meetings, trial steering committee, local health events/health fairs, newsletters, presentations to government bodies for information dissemination. These activities will be carried out throughout the project lifecycle and post-study close out.

e) Community advisory boards and communities in which the study is implemented

In the 2 study districts (Sekhukhune and Ekurhuleni), the Aurum institute has community advisory boards for research studies who help advise on current and future studies. The committees comprises of social workers, community workers, youth representatives, ministers of religion, government representatives, traditional healers, NGO representatives and ward councilors. These meetings are conducted on a monthly basis and these cadres are Aurum's route to the communities. The team will also use local health events or health fairs to get the information out to the community. These activities will be carried out throughout the project lifecycle and post-study close out.

f) Researchers, external experts and other community HCT providers

For this audience, the team will publish peer reviewed articles in high impact international and local South African journals. Poster and oral presentations will also be made at international (IAS, CROI) and local conferences (SA HIV Conference). Research summary documents (key findings and fact sheets) and press conferences will also be used for dissemination. These activities will be carried out throughout the project lifecycle and post-study close out.

8 STUDY MANAGEMENT

8.1 Aurum Institute

Aurum Institute has implemented large HIV care, ART, and HCT programs, has performed high impact operational research, and has conducted large clinical trials. Aurum's achievements include a cluster-randomized trial of TB preventive therapy among over 80,000 mine workers, ART delivery to 20,000 patients, health systems strengthening with 67 public sector primary health clinics, and operation of three clinical trials units for HIV prevention and TB treatment trials. Aurum is also a major partner to the Government of South

Africa in providing health system strengthening and direct services through US \$27 million from PEPFAR in 2011-2012 and US \$2 million from the Global Fund. Through research and implementation work, Aurum has built local capacity, community ties, and knowledge to successfully conduct large implementation science projects. In addition, as a South African institution, Aurum is building local capacity in program management and implementation research. The Aurum Institute is an ideal setting for completing the proposed implementation science research because it has an HCT program that tests a large number of patients, making it feasible to enroll adequate sample sizes, has a close working relationship with the Department of Health, including with HIV care provision; and has an excellent record of research success.

8.2 Project organogram

The project implementation team, which represents a smaller group of the co-investigators, will oversee project implementation including roll-out of interventions and adherence with planned milestones. Initially meetings will be conducted weekly and subsequently monthly.

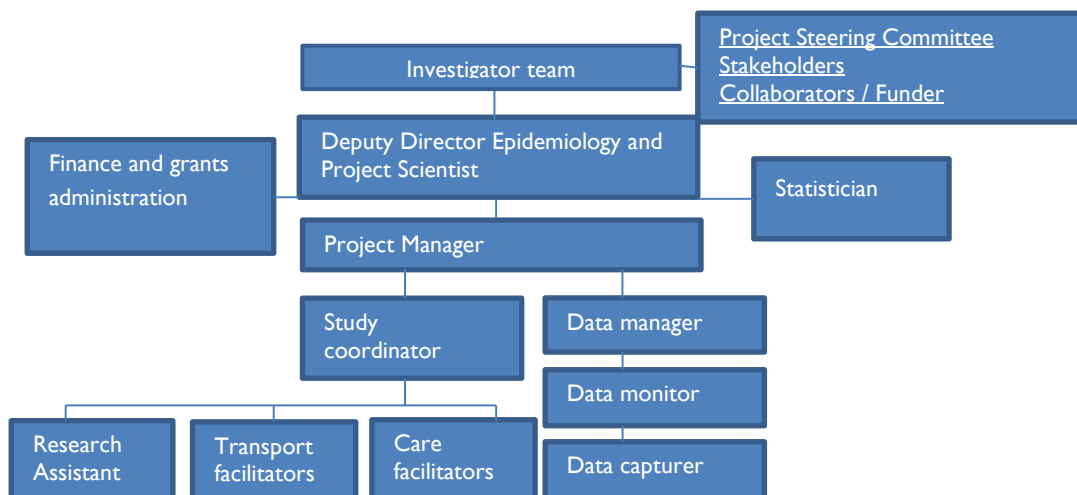


Figure 8.1: Study organizational structure

8.2.1 Operations team

The operational team is comprised of the following (Figure 6):

- Project Scientist: to provide technical oversight and expertise
- Deputy Director of Epidemiology: to provide guidance to the Project Manager and to ensure that standards are maintained
- Project Manager: is responsible for the day-to-day management of the project
- Project Coordinator: to ensure liaison with study sites
- Project Administrator: to oversee project administration issues
- Research Assistants: to obtain informed consent and follow up of participants

- **Data Manager:** is responsible for data collection and management, including data cleaning
- **Statistician:** to provide the randomization list, statistical and trial design input and oversee statistical analysis;
- **Co-Investigator:** responsible for clinical and economic aspects of study implementation and analysis
- **Health economist:** responsible for oversight of economic analysis and outcomes modeling
- **Management Accountant:** oversee expenditure and compilation of cost data

The operational team will meet weekly. The weekly meetings will be chaired by the Project Manager.

8.3 Investigators

Dr. Salome Charalambous MBBCh, MSc, is a South African and the Director of Research at the Aurum Institute. She leads a portfolio of research including multiple clinical trials, outcome studies, and operational research (approximately USD 6 million in 2010-2011), and has contributed 35 papers to the field. She formerly headed the Aurum HIV and TB care programs with 17 million USD of combined PEPFAR funding. Among current relevant projects, she is currently PI on a CDC funded study assessing the use of care facilitators to link released prison inmates into HIV care following release from prison. Salome will be leading the proposed study. **Prof. Gavin Churchyard, MBBCh MMED, FCP PhD** is a South African and the CEO of the Aurum Institute. He has pioneered population-based research including several large clinical trials of TB diagnosis and prevention including a Bill and Melinda Gates Foundation funded cluster-randomized trial of mass isoniazid delivery. He has published 90 articles on HIV and TB prevention and treatment. He will assist with study design and with engaging with government regarding findings of policy importance. **Tonderai Mabuto, MSc** is a Master's level epidemiologist with experience in operational research, implementation science, programme evaluation and participant recruitment to link individuals who test HIV positive to HIV care. He is also the principle investigator of a qualitative study on entry-into-care following HCT. He will manage day-to-day aspects of the study. **Dr. Christopher Hoffmann, MD, MPH, MSc** is an Infectious Diseases specialist, Senior Scientist at Aurum, and an Assistant Professor at the Johns Hopkins University School of Medicine. He is based at the Aurum Institute in Johannesburg, South Africa and has been working with Aurum on operational research since 2005. Dr. Hoffmann is experienced with study design, statistical analysis, decision analysis and economic modeling. He plays an important role in study design, economic analysis, and capacity development at Aurum. He has authored 5 book chapters and published 20 articles related to HIV care and treatment issues. He has also developed a state transition model for the effects of delays in cART initiation. Dr. Hoffmann will provide analytic support, outcomes and health economic modeling, and clinical expertise regarding HIV treatment. **Dr. Katherine Fielding, PhD** is a senior lecturer in medical statistics at the London School of Hygiene Tropical Medicine. She has been an author on over 70 papers related to TB and HIV management and has collaborated on Aurum research projects since 2000. Dr. Fielding is an expert in clinical trials regarding HIV and TB with special expertise in multi-site and

community-based trials. **Dr. David Dowdy, MD, PhD** is an assistant professor at the Johns Hopkins University Bloomberg School of Public Health and an expert on outcomes modeling related to HIV and TB, particularly in costing and modeling the impact of interventions in resource-limited-settings.

8.4 Management and staffing

The key personnel have all been involved in managing research projects. The Principal Investigator, **Dr Salome Charalambous** has managed PEPFAR implementation of ART and HIV prevention from 2004 to 2010 at Aurum, as well as implemented an employee HIV care and ART program within an industrial company that served approximately 20,000 employees with pre-ART care and 10,000 employees on cART. Dr. Charalambous presently oversees all the research activities at Aurum, including a large clinical trials unit and several large implementation studies. As noted above, Dr. Charalambous has led several studies and has contributed multiple publications to the field of HIV care and HIV operational research. **Prof. Gavin Churchyard** and **Dr. Katherine Fielding** are co-PIs on a large 7 year study of isoniazid preventive therapy among gold miners. This study has successfully completed all enrollment, follow-up, and endpoint assessment. Preliminary results were reported at the Conference for Retroviruses and Opportunistic Infections in Seattle in March 2012. **Prof. Churchyard** will contribute to stakeholder management and study design. **Dr. Fielding** is a leading expert on trial design and statistical interpretation of innovative strategy trials and implementation science. This includes the isoniazid prevention trial, a trial of accelerated ART and TB treatment among ART initiators (a US \$5 million study funded by UK MRC and DFID), and a study evaluating strategies to improve HIV and TB care integration (funded by CDC). **Dr. Christopher Hoffmann** has contributed multiple publications related to HIV care outcomes and implementation in resource-limited-settings. In addition, he has developed decision analytic models to inform care priorities and policy. **Mr. Tonderai Mabuto** has managed multiple studies with multiple staff accountable to him. His input and leadership has contributed significantly to the success of these studies. One is a TB and HIV testing study with care referral among South African transport workers and another is to describe patterns of HCT clients and outcomes following HCT. In addition, he is currently completing a qualitative study of barriers and facilitators to entry-into-care following testing HIV positive at HCT.

8.5 Performance monitoring and evaluation plan

We based the performance management plan (PMP) on the established results framework. The aims of the PMP were aligned with those developed by the USAID. Primarily; to ensure that the project team and stakeholders would understand (i) what was being measured, (ii) the data collection methodology, (iii) the tasks and schedules associated with each indicator, (iv) data analysis plan. We used the terminology of

performance indicators and defined these as characteristics used to measure intended changes as defined by our project results framework (ADS 200/6).

For each development objective, intermediate results and output we defined and tabulated the following variables:

1. Name of the performance indicator
2. Definition of the performance indicator
3. Unit of measurement for the performance indicator
4. Data sources for the performance indicator
5. Data collection methods for the performance indicator
6. Frequency and schedule of collection for the performance indicator
7. Responsibility for data acquisition
8. Baseline value for the performance indicator
9. Project target for the performance indicator

8.6 Environmental hazards

No materials used or procedures performed as parts of this proposed research are hazardous to research personnel or the environment.

8.7 Gender & children

The proposed study will recruit both males and females and will not discriminate on the basis of gender, thereby avoiding any gender inequities or disparities in services delivered. The specific strategies may have important gender-related effects: the care facilitator will assist with issues of disclosure, stigma, and gender-based violence, all issues that may impact HIV-infected women more than men. Men, a marginalized group in terms of cART provision, may also develop improved attitudes towards seeking healthcare and benefit from improved rates of entry-into-care.

This study is limited to adults (age 18 and older) for two reasons: (1) HIV counseling and testing programs are focused on diagnosing HIV among adults. Diagnosis of HIV among children optimally occurs during well child visits (among HIV exposed infants) and other clinical encounters where it is part of routine care in South Africa. Adults have much less contact with the health care system and thus are in more need of dedicated HCT services. (2) The proposed entry-into-care strategies have been developed around the HIV-infected individual. Increased entry-into-care among children requires a different focus – a focus on the children’s care providers (parents, grandparents, etc.).

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S2 Appendix Subgroup and Mortality Results

Subgroup analysis for self-reported 90 day entry-into-care

Subgroup analysis for verified 90 day entry-into-care

Mortality analysis

Subgroup Analyses for Primary Outcome: 90 day self-reported entry-into-care

		Standard of care	POC-CD4 count	POC-CD4 count + care facilitation	POC-CD4 count + transport reimbursement
Sex					
Men	HR (95% CI)	1	1.1 (0.82, 1.4)	1.2 (0.91, 1.5)	0.99 (0.76, 1.3)
	p-value				
Women	HR (95% CI)	1	1.0 (0.84, 1.2)	1.1 (0.87, 1.3)	0.97 (0.79, 1.2)
	p-value				
Interaction: p-value			0.8	0.5	0.9
CD4 count¹					
CD4<350	HR (95% CI)	NA	1	1.2 (0.98, 1.6)	1.0 (0.78, 1.3)
	p-value				
CD4 ≥350	HR (95% CI)	NA	1	0.98 (0.80, 1.2)	0.95 (0.77, 1.2)
	p-value				
Interaction: p-value				0.1	0.7
Urban & peri-urban /rural					
Urban/peri-urban	HR (95% CI)	1	0.99 (0.80, 1.2)	1.0 (0.82, 1.2)	0.93 (0.75, 1.1)
	p-value				
Rural	HR (95% CI)	1	1.1 (0.87, 1.4)	1.2 (0.98, 1.6)	1.0 (0.81, 1.3)
	p-value				
Interaction: p-value			0.4	0.2	0.5
Distance to clinic (km)					
<5km	HR (95% CI)	1	1.0 (0.84, 1.3)	1.0 (0.81, 1.2)	1.0 (0.81, 1.2)
	p-value				
≥5km	HR (95% CI)	1	1.1 (0.87, 1.4)	1.2 (0.98, 1.6)	0.97 (0.76, 1.2)
	p-value				
Interaction: p-value			0.7	0.7	0.8
Age (years)					
≤30yrs	HR (95% CI)	1	1.0 (0.80, 1.3)	1.0 (0.77, 1.3)	0.93 (0.71, 1.2)
	p-value				
>30yrs	HR (95% CI)	1	1.0 (0.86, 1.3)	1.2 (0.97, 1.4)	1.0 (0.82, 1.2)
	p-value				
Interaction: p-value			0.7	0.3	0.9
Transport cost (US\$)					
≤US\$2	HR (95% CI)	1	1.2 (0.98, 1.4)	1.1 (0.90, 1.3)	1.0 (0.87, 1.2)
	p-value				
>US\$2	HR (95% CI)	1	0.90 (0.63, 1.3)	1.0 (0.75, 1.5)	1.0 (0.73, 1.4)
	p-value				
Interaction: p value			0.2	0.9	0.9
Presence of symptoms					

Routine testing / other	HR (95% CI)	1	1.0 (0.86, 1.2)	1.1 (0.94, 1.3)	0.94 (0.79, 1.1)
	p-value		0.8	0.2	0.5
Symptoms present	HR (95% CI)		1.2 (0.77, 1.8)	1.0 (0.68, 1.6)	1.2 (0.78, 1.8)
	p-value		0.5	0.8	0.4
Interaction: p value			0.5	0.8	0.3
Employment status					
Employed	HR (95% CI)	1	1.0 (0.83, 1.3)	1.1 (0.9, 1.4)	0.92 (0.72, 1.2)
	p-value		0.7	0.3	0.5
Other	HR (95% CI)	1	1.0 (0.83, 1.3)	1.1 (0.87, 1.3)	1.0 (0.82, 1.2)
	p-value		0.8	0.5	0.9
Interaction: p value			0.9	0.7	0.6

¹ as POC-CD4 was not done in the SoC arm intervention arms POC-CD4 count + care facilitation and POC-CD4 count + transport voucher are compared to POC-CD4 count alone

Subgroup Analyses for Primary Outcome: 90 day verified entry-into-care

		Standard of care	POC-CD4 count	POC-CD4 count + care facilitation	POC-CD4 count + transport reimbursement
Sex					
Men	HR (95% CI)	1	1.2 (0.88, 1.5)	1.5 (1.1, 2.1)	1.0 (0.70, 1.4)
	p-value		0.3	0.01	0.9
Women	HR (95% CI)	1	1.0 (0.76, 1.3)	1.3 (1.0, 1.6)	1.1 (0.88, 1.5)
	p-value		0.8	0.05	0.3
Interaction: p-value			0.4	0.4	0.6
CD4 count¹					
CD4<350	HR (95% CI)	NA	1	1.4 (1.1, 1.8)	1.1 (0.84, 1.5)
	p-value			0.01	0.4
CD4 ≥350	HR (95% CI)	NA	1	1.2 (0.92, 1.6)	1.0 (0.77, 1.4)
	p-value			0.2	0.8
Interaction: p-value				0.5	0.7
Urban & peri-urban /rural					
Urban/peri-urban	HR (95% CI)	1	1.0 (0.76, 1.3)	1.2 (0.95, 1.6)	1.0 (0.76, 1.3)
	p-value		0.9	0.1	0.9
Rural	HR (95% CI)	1	1.1 (0.83, 1.6)	1.5 (1.1, 2.1)	1.2 (0.87, 1.6)
	p-value		0.4	0.004	0.7
Interaction: p-value			0.5	0.3	0.4
Distance to clinic (km)					
<5km	HR (95% CI)	1	1.2 (0.92, 1.6)	1.3 (1.0, 1.7)	1.1 (0.82, 1.5)
	p-value		0.2	0.05	0.5
≥5km	HR (95% CI)	1	0.9 (0.65, 1.2)	1.4 (1.0, 1.8)	1.1 (0.81, 1.5)
	p-value		0.5	0.04	0.5
Interaction: p-value			0.2	0.8	0.9
Age (years)					
≤30yrs	HR (95% CI)	1	1.1 (0.75, 1.6)	1.5 (1.0, 2.1)	1.2 (0.84, 1.8)
	p-value		0.6	0.04	0.3
>30yrs	HR (95% CI)	1	1.0 (0.82, 1.3)	1.3 (1.0, 1.7)	1.0 (0.81, 1.3)
	p-value		0.7	0.02	0.7
Interaction: p-value			0.8	0.7	0.5
Transport cost (US\$)					
≤US\$2	HR (95% CI)	1	1.2 (0.93, 1.5)	1.4 (1.1, 1.8)	1.2 (1.0, 1.6)
	p-value		0.02	0.007	0.04
>US\$2	HR (95% CI)	1	0.78 (0.49, 1.2)	1.2 (0.75, 1.8)	0.93 (0.6, 1.4)
	p-value		0.6	0.5	0.8
Interaction: p value			0.1	0.4	0.2
Presence of symptoms					
Routine testing / other	HR (95% CI)	1	1.1 (0.87, 1.4)	1.4 (1.1, 1.7)	1.1 (0.87, 1.4)
	p-value		0.5	0.002	0.4
Symptoms present	HR (95% CI)		0.90 (0.53, 1.5)	1.2 (0.74, 2.0)	1.0 (0.62, 1.8)

	p-value		0.7	0.4	0.4
Interaction: p value			0.5	0.6	0.9
Employment status					
Employed	HR (95% CI)	1	0.91 (0.66, 1.2)	1.3 (0.98, 1.8)	0.99 (0.71, 1.4)
	p-value		0.6	0.3	0.5
Othe	HR (95% CI)	1	1.2 (0.91, 1.6)	1.4 (1.1, 1.8)	1.2 (0.89, 1.5)
	p-value		0.2	0.01	0.3
Interaction: p value			0.2	0.9	0.4

Mortality and study arm

	Standard of care	POC-CD4 count	POC-CD4 count + care facilitation	POC-CD4 count + transport reimbursement
Mortality				
365 days				
Deaths, proportion (number of deaths)	0.018 (11)	0.013 (8)	0.015 (9)	0.020 (12)
Hazard ratio (95% confidence interval))*	1	0.70 (0.28, 1.7)	0.8 (0.33, 1.9)	1.1 (0.48, 2.5)
P-value, compared to standard of care		0.4	0.6	0.8

* hazard ratio adjusted for randomization strata