Integrated Model of Cancer Control for Early Detection and Treatment in Adolescents and Young Adults Living with HIV in Zambia: Protocol for a Cluster-Randomized Control Trial

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[1]Implenomics Dover US
[2]Population Council Lusaka ZM
[3]Clinical and Radiation Oncology Society of Zambia (ZASCRO) Lusaka ZM
[4]RTI International Durham US

Corresponding Author:
Sanjana Batabyal MPH
Implenomics
8 The Green Suite #6172
Dover
US

Abstract

Background: Zambia has one of the highest rates of prevalence of HIV among adolescents and young adults living with HIV (AYAHIV) in sub-Saharan Africa, who, as of 2023, represent half of all new HIV cases annually. Compared to their peers who are HIV negative, AYAHIV are at an increased risk of developing cancer. The most frequently diagnosed cancers among AYAHIV in Zambia are cervical cancer (CC), Kaposi Sarcoma (KS), and non-Hodgkin's Lymphoma (NHL). Premature cancer mortality among AYAHIV is driven by late-stage presentation and poor treatment adherence. The objective of this proposed research is to develop and test an integrated model of cancer control for AYAHIV that can be delivered as an embedded component in existing HIV treatment programs in primary care facilities and linked with specialist treatment in cancer centers.

Methods: We propose a cluster randomized control trial to compare the AYAHIV Role-based Responsibilities for Oncology-focused Workforce (ARROW) program with a one-time education campaign. The ARROW Program consists of interventions at three levels. At the individual level, peer counselors will educate AYAHIV through one-on-one and group education sessions, provide emotional support, and offer care coordination and linkages with the clinical team. At the provider level, collaborative education and training among HIV and oncology workforce will be facilitated. At the health system level, the ARROW Healthcare Collaborative will bring together administrators and policy makers to address system-level barriers. The study will recruit 3,600 AYAHIV across 18 HIV treatment facilities in Lusaka, Zambia between the ages of 15 and 39, who have been on ART for at least 6 months, and are not pregnant in its early detection cohort and 500 AYAHIV who have been diagnosed with CC, KS, or NHL in its cancer treatment cohort. We will also conduct economic evaluations to assess the cost-effectiveness of the ARROW program.
Discussion: The ARROW cohort recruitment has begun, and results pertaining to the 12-month endpoints will be available in early 2026. The ARROW program, if shown to be successful, will offer a model for improved linkages and integration between HIV and cancer services to improve cancer prevention, early diagnosis and treatment. Furthermore, ARROW can provide a framework for implementing expanded services, such as survivorship care, for AYAHIV.

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Author Affiliations:
[1] Implenomics, Dover, DE, USA
[2] Population Council, Lusaka, Zambia
[3] Clinical and Radiation Oncology Society of Zambia (ZASCRO), Lusaka, Zambia
[4] Research Triangle Institute (RTI), International, Research Triangle Park, NC, USA

Corresponding author: Sanjana Batabyal <Sanjana.Batabyal@implenomics.com>

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Trial Registration: ClinicalTrials.gov NCT06004011 (Registration Date: August 15th, 2023)

Keywords: Adolescents and young adults; HIV care; cancer treatment; early detection of cancers

Background

Adolescents and young adults (AYA), those from 15 to 39 years of age, represent a growing share of people living with human immunodeficiency virus (HIV) worldwide. Zambia has one of the highest rates of prevalence of HIV among AYA in sub-Saharan Africa; as of 2023, there are approximately 90,000 AYA between the ages of 10 and 19 living with HIV, with only half that population receiving antiretroviral therapy (ART) [1]. The AYA population also accounts for half of all new recorded infections in the country [1]. Compared to their peers who are HIV negative, AYA living with HIV (AYAHIV) are at an increased risk of developing cancer [2-4]. Cancers most frequently diagnosed among AYAHIV in Zambia are Kaposi Sarcoma (KS), non-Hodgkin's Lymphoma (NHL), and cervical cancer (CC) [5-9]. Incidence of these cancers increases with lower CD4 cell count; therefore, adherence to ART is paramount [10]. Unfortunately, AYAHIV are among the most vulnerable groups with poor adherence to ART and there is no large-scale cancer control program to facilitate early diagnosis and completion of guideline-recommended treatments in Zambia [11,12].

An AYAHIV-focused cancer program tailored to the Zambian limited resource setting is needed to reduce premature mortality. Data on AYAHIV malignancies are sparse, but late-stage presentation, unplanned breaks from cancer treatment, and abandonment of treatment have been reported among young cancer patients in resource-limited settings [13-15]. These factors result in high morbidity and premature mortality among AYAHIV diagnosed with cancer. Late-stage presentation and lack of treatment adherence are key drivers of premature cancer mortality among AYAHIV in Zambia.

AYAHIV are a vulnerable population who face psychosocial issues, stigma, and comorbidities that affect their healthcare-seeking behavior [16]. AYAHIV with cancer in Zambia have unmet needs related to information about health risks, coping strategies for medication side effects, positive peer and family support, and activation of personal agency [17-21]. Further, during transition from the pediatrics to adult HIV clinics, many AYAHIV are lost to care [22-26]. Providers who specialize in HIV care and oncologists face barriers, such as time constraints, with regard to AYAHIV cancers and this inhibits their ability to deliver optimal care [27,28]. There are also no linkages for collaborative management of AYAHIV with cancer between primary care HIV providers and cancer specialists. At the health system level, some key barriers are weak referral systems and lack of standardized protocols to implement AYA-friendly care [29-33].

The Zambian guidelines recommend CC screening for all female AYAHIV who are sexually active, regardless of age [34]. However, screening among AYAHIV is low, despite the availability of free health care services. In a recent study less than 40% of AYAHIV had ever been screened for CC [18,35]. There are no screening tests available for KS or NHL, but increasing awareness of the risk factors and symptoms, along with physical exams, could reduce late presentation [13,30]. In fact, strategies to facilitate early detection of KS have shown promise in other African countries. A recent study in Uganda used education messaging (comic strip and video) to increase KS awareness and knowledge [36]. Furthermore, researchers in Zimbabwe developed a physical exam checklist to identify symptoms of KS [37]. Cancer Diseases Hospital, which is the main referral center for treatments in Zambia, has adopted the National Comprehensive Cancer Network's (NCCN) Harmonized Guidelines for Sub-Saharan Africa for on AYA oncology to optimize treatment. NCCN guidelines will be most effective when paired in tandem with adequate treatment adherence support for AYAHIV.

AYA-focused programs have been successful in other settings, especially in high-income countries. These programs use a variety of models to promote collaboration across multidisciplinary teams and

integrate medical and psychosocial care for AYA [38-40]. In Sub-Saharan African countries like Zambia, multiple barriers need to be addressed to facilitate early diagnosis in the primary care setting and to ensure receipt of full treatment course in cancer centers [41,42]. The objective of this proposed research is to develop and test an integrated model of cancer control for AYAHIV that can be delivered as an embedded component in existing HIV treatment programs in primary care facilities and linked with specialist treatment in cancer centers.

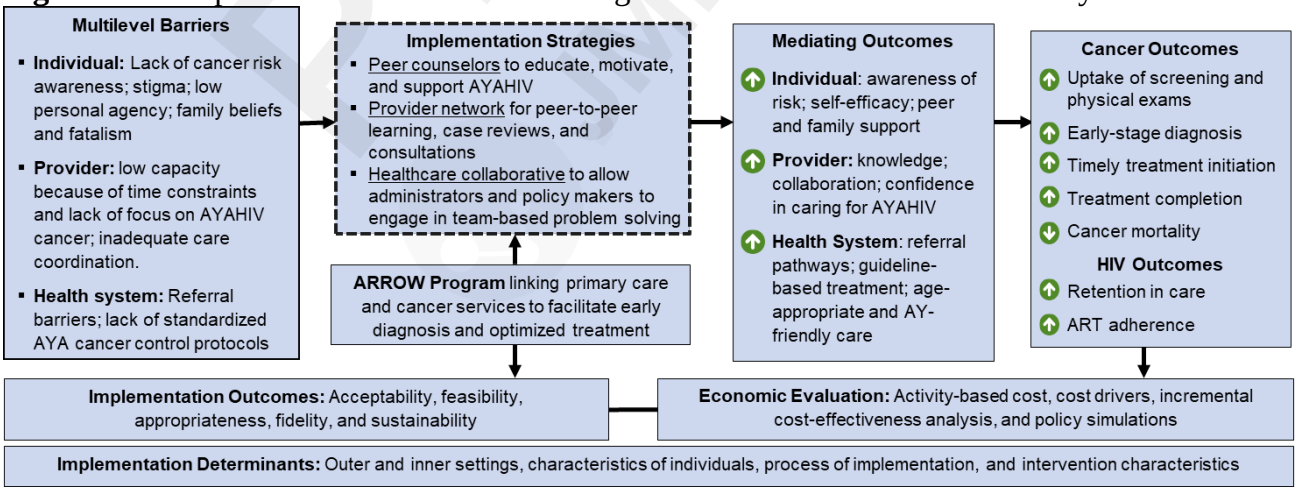
Methods

Overview and Conceptual Framework

We propose a program that embeds AYAHIV cancer control strategies into existing HIV treatment programs in primary care facilities and at cancer centers in Zambia by strengthening and supporting the existing clinical teams to optimize cancer care delivery. We used theory-informed multilevel strategies to create the **A**YAHIV **R**ole-based **R**esponsibilities for **O**ncology-focused **W**orkforce (ARROW) program to increase uptake of services for early diagnosis and improve compliance with cancer treatment for CC, KS, and NHL (Trial Registration: ClinicalTrials.gov NCT06004011). ARROW will utilize an evidence-driven approach to select low-cost, multilevel peer-to-peer support and learning strategies to address identified barriers and delineate roles played by HIV and cancer providers to deliver guideline-directed care for early diagnosis and cancer treatment. Each of the proposed strategies has been tested in the Zambian and Sub-Saharan African context and shown to be feasible [18,43-47].

Our overall approach is based on the evidence-based strategy of peer support for engagement and learning [48-56]. Figure 1 presents the theoretical framework, which is based on the socioecological model [57]. We have created the ARROW Program with strategies that focus on barriers at the individual, provider, and health system levels. These strategies are guided by the COM-B (capability, opportunity, motivation and behavior) model, in which capability (e.g., knowledge and cancer risk), opportunity (e.g., availability of high-quality screening and treatments), and motivation (e.g., self-efficacy and care-seeking behavior) interact to facilitate behavior change [57].

Figure 1 Conceptual framework for addressing barriers to reduce cancer mortality



Legend: AYAHIV: adolescents and young adults living with HIV; ART: Antiretroviral Therapy

Interventions

The ARROW Program is a holistic intervention that is meant to support HIV and cancer care at three different levels: individual, provider and health system.

Individual Level

There is growing evidence on the role peer support can play in addressing individual and interpersonal barriers to improve knowledge and encourage AYA to seek medical care [58-64]. We will place trained peer counselors (PCs) in HIV treatment facilities and at the Cancer Diseases Hospital to educate AYAHIV, provide emotional support, and offer care coordination and linkages with the clinical team. PCs will offer support for early diagnosis of cancers, completion of cancer treatment, and ART adherence as required. They will coordinate care with providers and serve as an extension of the clinical team by conducting physical exams to identify signs of KS and NHL and offering coping strategies for ART and chemotherapy side effects.

A total of 21 PCs, 10 males and 11 females between the ages of 20 and 39, will be recruited. Of that, 18 PCs (9 men and 9 women) will receive training for placement in HIV treatment centers. The remaining 3 PCs (1 man and 2 women) will be posted to Cancer Diseases Hospital. The recruitment of more female PCs is due to the heavy burden that CC places on the healthcare system. Our existing 3-week training curriculum, from a prior study conducted by the research team, will be tailored for PCs and will include training on appointment tracking systems [18]. The curriculum will include standardized operating procedures for implementing the group education sessions to include additional details on cancer risk, early diagnosis approaches, and optimal treatments. Those assigned to Cancer Diseases Hospital will receive training on helping AYAHIV deal with treatment side effects and assist with adherence to ART while undergoing cancer treatment. PCs will conduct site visits of the HIV facilities and Cancer Diseases Hospital to become familiar with the staff, layout of the clinics, and services available.

Table 1 summarizes the four core PC roles and their corresponding activities. PCs will offer six group education sessions at each ARROW HIV facility per month (one module each month) for the first 12 months along with one-on-one education. For the remaining follow-up period, PCs will offer one-on-one education as needed. All other activities will continue throughout the trial.

Table 1 Four key functions of PCs

	HIV Treatment Facility	**Cancer Diseases Hospital**
HIV and cancer knowledge	Group and one-on-one education on cancer early diagnosis and ART adherence	One-on-one education on cancer treatment and ART adherence; some group sessions

Social and emotional support	Group sessions and individual meetings to discuss coping with stigma, family stressors, and side effects (ART or cancer treatment)	
Care-seeking behavior	Motivational interviews; PCs offer convenient times for physical exam; reminder phone calls before visits	Documenting treatment plan; tracking of visits to remind AYAHIV about visits; identifying and addressing barriers
Care coordination	Accompany AYAHIV to referral visits; facilitate delivery of results to HIV care team; inform AYAHIV on next steps	Ensure cancer care team is aware of any barriers to adherence; facilitate communication with HIV care team

Abbreviations: ART Antiretroviral therapy, *PC* Peer counselor, *AYAHIV* Adolescents and young adults living with HIV, *HI*V Human immunodeficiency virus

Educational materials will be made for the two study arms for the randomized control trial by adapting existing group and one-on-one educational materials, such as training modules previously tested for KS awareness or NCCN AYA Guidelines for Patients. These materials will be presented at pre-testing workshops. Trained facilitators will present materials to ensure they are age-appropriate by assessing participants' ability to understand, whether the topics and contents address key issues faced by the age group, and whether AYAHIV can embrace and follow the solutions or advice offered. Using the feedback received, we will finalize the modules and brochure. All adapted education materials for AYAHIV will be available in English, Bemba, Nyanja, and Tonga. Provider guidance documents will be available in English, as in past projects; all Zambian providers are fluent in English.

A treatment plan based on NCCN treatment and survivorship plans will be developed for study participants at Cancer Diseases Hospital. PCs will update AYAHIV treatment plans through the treatment course which will serve as a comprehensive patient record that can also be placed in the patient file at the HIV treatment center that the AYAHIV will return to after treatment completion.

Provider Level

Team-based care is critical for optimal oncology care delivery [63,64]. Formalized communication channels, collective learning, and clear team roles are the cornerstone of collaborative care teams [65,66]. The ARROW Provider Network will use a tailored Project ECHO (Extension for Community Healthcare Outcomes) approach to link pediatric and adult healthcare providers who specialize in HIV care in the primary care facilities with counterparts at Cancer Diseases Hospital to enable peer-to-peer learning, review of patient cases, and expert consultations [46].

Guidance documents and brochures will be created for providers by inviting a mix of pediatric and adult-care providers to co-creating workshops. These materials will contain background information, AYA-friendly care delivery, age-appropriate engagement with AYAHIV, monitoring of ART adherence, flow charts with referral pathways for early diagnosis, process steps to implement guideline-recommended cancer treatment for AYAHIV, documentation of services provided (for example, in the SmartCare electronic health record, which is used in HIV facilities and capture visit details, medications, and laboratory tests), and a charter with roles and responsibilities for clinical teams in the HIV treatment centers and those at Cancer Diseases Hospital. Facilitators will use NCCN Sub-Saharan African harmonized guidelines for each cancer, along with the AYA guidelines, and create an AYAHIV-focused guidance documents tailored to the Zambian setting.

Providers will also receive in-person training at each of the nine HIV facilities selected to implement the ARROW program and at Cancer Diseases Hospital before initiating the implementation trial. These trainings will also include sessions on understanding stigma faced by AYAHIV, delivering age-appropriate and AYA-friendly care, and best practices for communication with AYAHIV using previous training tools [17]. All HIV providers (both pediatric and adult) will be encouraged to attend a session. We will hold additional training as needed, including refresher trainings sessions during the 36-month trial.

We will initiate activities to facilitate collaborative learning and coordination by hosting (a) monthly peer-to-peer virtual sessions with presentations from Zambian and international physicians working to improve AYA cancer care, AYAHIV case reviews, and expert consultation panels to address specific questions from the provider network; (b) an annual in-person meeting in Lusaka to review progress and next steps; and (c) an in-facility biannual seminar with adult and pediatric teams on AYAHIV-specific issues.

Health System Level

We will initiate the ARROW Healthcare Collaborative, which will bring together health system administrators and Zambian Ministry of Health policy makers to foster team-based problem solving and implementation of solutions to address system-level barriers (e.g., barriers related to referrals). We will also employ a user-centered design process to co-create education materials and guidance documents to implement ARROW.

We will invite 6 health care administrators from Lusaka province and 4 Ministry of Health policymakers to join the Collaborative to foster team-based problem solving. These individuals will meet quarterly to review implementation challenges related to referral pathways and other system-level barriers to receiving services to facilitate early diagnosis and optimal cancer treatment. Each meeting will end with clear action steps towards resolving the barriers and procedures that will be used to monitor the implementation of the proposed solutions. The first meeting of the Collaborative will take place 6 months before the start of the trials to allow adequate time to identify and address any gaps identified through the readiness assessment. The reduction in barriers will benefit not only ARROW program participants but all AYAHIV in Lusaka province.

Randomized Control Trials

Overall Study Design

We will compare the ARROW program to a one-time education campaign that gives informational brochures to AYAHIV and HIV providers. Given the acute need for AYAHIV cancer control strategies to reduce premature mortality, planning consultations with community stakeholders deemed it unethical to use “usual care” as the comparison arm. We will, therefore, test the hypothesis that the ARROW Program will be more effective than a one-time education campaign (education brochures to AYAHIV and HIV providers) in increasing care received by AYAHIV to facilitate early diagnosis (physical examination for KS and NHL, CC screening; timely referrals) and in improving adherence to treatment among AYAHIV diagnosed with cancer. We will also assess implementation outcomes, based on the Proctor framework, analyze determinants of implementation (based on the Consolidated Framework for Implementation Research [CFIR]), and conduct economic evaluation of the ARROW Program [67,68].

Early Detection Cohort: We propose a cluster randomized study implemented in 18 HIV treatment facilities in Lusaka province. Three facilities serving each type of regional population (urban, peri-urban, or rural populations) will be randomly assigned to a study arm: ARROW program or one-time education. Overall, nine facilities will be assigned to each arm of the trial, with data collection at baseline and at 12, 24- and 36-month follow up. At each of the 18 clinics, we will enroll 100 males and 100 females for a total of 3,600 participants in the early detection cohort. The 200 AYAHIV per facility will be selected by first reviewing the HIV register and identifying AYAHIV who meet study inclusion criteria: 15 to 39 years of age, on ART for at least 6 months, not pregnant, and with no pending plans to move from current residence during the 3-year study duration. For all 3,600 participants, we will collect baseline data and capture information on study endpoints from the SmartCare system and the supplemental data collected by PCs and trained study data collectors (e.g., tracking referrals for all participants and obtaining results of biopsies).

Cancer Treatment Cohort: This will take place entirely at Cancer Diseases Hospital, with some patients being recruited from the University Teaching Hospital. A total of 500 AYAHIV who have been diagnosed with CC, NHL, or KS will be recruited into the study, with 250 patients in each trial arm (i.e., one-time educational campaign vs. ARROW intervention). Patients will be surveyed on an annual basis at 12, 24, and 36 months. Trained data collectors will consent and enroll AYAHIV aged 15 to 39 years. We will be aiming for the following targets for each cancer type: 250 with CC, 150 with KS, and 100 with NHL (with overall equal number of male and female AYAHIV for KS and NHL). While AYAHIV who are pregnant will be excluded, as they require specialized care, AYAHIV who become pregnant during the trial period will remain enrolled in the study; CC screening and physical examination for KS and NHL will be offered based on Zambian guidelines pertaining to pregnancy.

We hypothesize that, by facilitating peer support to address barriers and gaps at multiple levels, the ARROW program will be more effective than the one-time education campaign, but more expensive as well. As shown in Figure 2, we will simultaneously conduct separate randomized trials at the HIV treatment facilities and at Cancer Diseases Hospital. The trials will be initiated upon completion of the pre-implementation preparation activities. We will then embed PCs into the care teams at the HIV facilities and Cancer Diseases Hospital and initiate the planned implementation activities of the Provider Network in the ARROW Program arm. The comparison arm will receive the one-time education campaign: providers at the HIV facilities (particularly physicians and nurses) will receive a brochure with key guidance for early diagnosis of AYAHIV cancers, and AYAHIV upon recruitment will also receive education brochures at both the HIV facilities and at Cancer Diseases Hospital. The Health Care Collaborative will continue to meet as planned on a quarterly basis.

Figure 2. Experimental design and sample sizes

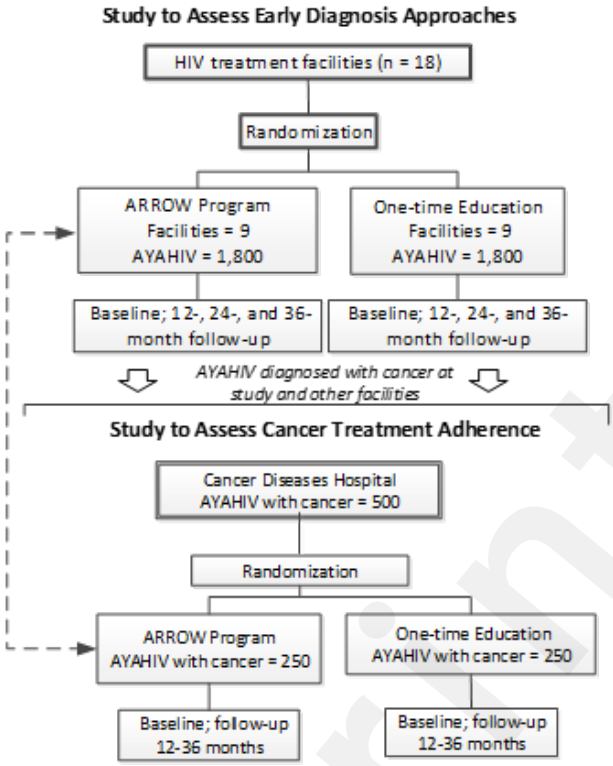


Figure 2 Legend: ARROW: AYAHIV Role-based Responsibilities for Oncology-focused Workforce; AYAHIV: adolescents and young adults living with HIV

Study Endpoints

Early Detection Cohort: We will assess effectiveness based on dual primary endpoints. The first primary endpoint is the proportion who complete a physical exam visit for KS and NHL and the proportion who are up-to-date with CC screening (females only) at 12 months. The second primary endpoint is the proportion who complete recommended follow-up supplemental or diagnostic procedures (within 3 months of receiving follow-up referral), those who initiate cancer treatment (within 3 months of diagnosis), and those who complete additional cancer detection visits, over 36 months. The secondary endpoint, evaluated at 36 months, is the proportion diagnosed at an early stage (among those diagnosed with KS, NHL, and CC). We will likely have few cancer cases in the study facilities. Therefore, these findings will not be conclusive but will offer insights into the potential impact of ARROW program on facilitating diagnosis at an early stage.

Cancer Treatment Cohort: The primary endpoint is the proportion who are adherent to cancer treatment (complete all treatment modalities as prescribed; 2-week delays will be allowed) at 12 months after diagnosis, the secondary endpoint is the proportion alive at 12 months after diagnosis, and the tertiary endpoint is the proportion with recurrence at 24 and 36 months (among those with 24- and 36-month follow-up).

For all AYAHIV, we will report adherence to ART (proportion filling prescriptions at least every 3 to 6 months) and viral load at 12, 24, and 36 months. Viral load testing is generally conducted at least annually for AYAHIV as part of routine guideline recommended practice. We will reinforce the need for regular viral load testing as part of provider training and have set aside funds to conduct viral load testing for study participants for whom this information is unavailable in the medical record.

Sample Size and Recruitment

Early Detection Cohort: We will use stratified random sampling to select an equal number of male and female participants and a mix of AYAHIV with perinatally and behaviorally acquired HIV. In terms of age distribution, 20% of the sample will be 15 to 19 years of age, 20% will be 20 to 24 years of age, and 60% will be 25 to 39 years of age. We will oversample AYAHIV in each stratum to account for AYAHIV who may not meet inclusion criteria or who decline to participate. HIV facility staff will contact AYAHIV or consenting adults (for 15- to 17-year-olds) to discuss the study, and those interested will meet with trained data collectors who will assess eligibility and obtain consent or assent. The sample size was calculated assuming conventional specifications (alpha = .025 for each endpoint, two-sided tests), based on the dual primary endpoints and allowing for the detection of an absolute 20-percentage point improvement in the primary endpoints, our minimum threshold to consider the ARROW program successful. For the one-time education arm, given the current low level of uptake of early diagnosis services, we estimate uptake of physical exams to be about 15% and CC screening to be about 20% at 12 months. With our proposed sample size of 3,600, we will be able to detect a 20% difference in uptake of physician exam (35% in ARROW arm) with over 90% power and CC screening (40% in ARROW arm) with over 85% power. We can achieve this even after accounting for up to 10% attrition at 12 months (a prior study conducted by the research team achieved this retention rate without the level of active participant contact planned for this study) [69]. We estimate that the interclass correlation coefficient (ICC) will be in the range of 0.03 to 0.05 because ICCs for binary data are typically quite small, especially when physical exams and screening uptake are very low [70].

Cancer Treatment Cohort: We will use stratified random assignment to place patients in each arm of the trial. Once we have enrolled 10 patients with each type of cancer, we will randomly assign half to the ARROW program and the other half to the one-time education arm. All patients will have a minimum of 12 months follow-up, and some will have up to 36 months of follow-up. Data will be collected at baseline and then annually for the three-year duration of the trial from the AYAHIV through surveys and by abstracting information from Cancer Diseases Hospital records. The sample size was calculated using conventional specifications (alpha = 0.05, two sided tests) based on the primary endpoint and allowing for an absolute 15-percentage point improvement; the estimated current level of adherence is 75%, which will increase to at least 90% with the ARROW program. With 250 patients in each arm, we will have more than 90% power to detect this difference.

Data Collection

In the HIV treatment facilities, we will generate electronic data files for the study cohort, and in other settings, such as referral facilities and Cancer Diseases Hospital, the study team will abstract data from electronic databases or paper files. We will also conduct surveys to collect data from AYAHIV and providers. The PCs will document their interaction with AYAHIV in the PC tracking tool, and provider participation in the ARROW Provide7-8r Network will be captured in the study database. These details will be used to determine the “dose” of the ARROW program. All data will be collected by trained data collectors, who will undergo continual monitoring, and study coordinators, who will confirm fidelity to protocol specifications by random in-person review. See Table 2 for endpoint definitions and biological, self-report, and clinic records data collected at baseline and 12-, 24-, and 36-month follow-ups.

Table 2 Data collection at baseline, 12 months, 24 months, and 36 months

Constructs/Measures	Instrument and Specification	Source	Timing
Data elements for primary, secondary, & tertiary endpoints—HIV and cancer care continuum			
Proportion completing physical exam (KS &	Confirmation of services will be based on clinical records and PC	Biological,	12m, 24m,

NHL) and up-to-date with CC screening	tracking tool (primary endpoint at 24m)	imaging, & clinical procedures identified through clinic record & study database	& 36m
Proportion completing diagnostic tests & initiating treatment in ≤ 90 days	Measured as days from referral for testing and cancer diagnosis, respectively; based on chart review & study data		24m & 36m
Proportion completing repeat exams & screening at recommended interval	Screening every 2 years for CC and annual exam (especially when CD4 < 100) based on Zambian guidelines		36m
Proportion with early-stage diagnosis[1]	Stage I or II for NHL & CC; good risk for KS[2]		36m
Proportion adherent to cancer treatment[1]	Complete cancer treatment modalities as recommended		12m after diagnosis
Proportion alive at 12m after diagnosis[1]	Follow-up conducted by PCs and entered in study database		
Proportion with recurrent disease[1]	AYAHIV with cancer who experience recurrence		36m
Proportion adherent to ART & viral load	Prescription filled every 3–6 months; blood test		Annually
HIV status, demographics, mediating outcomes, intervention dose, & clinical services			
HIV status and diagnosis date	Perinatally or behaviorally infected; CD4 count	Clinic record	Baseline
Demographics & socioeconomic status	RTI AYA Zambia survey	Self-report	Baseline
Self-efficacy (AYAHIV)	Generalized Self-Efficacy Scale [7171]	Self-report	Baseline, 12m, 24m, & 36m
Social support & mental health (AYAHIV)	Brief Social Support & Patient Health Questionnaires [71,727172]		
HIV & cancer stigma (AYAHIV)	Anticipated stigma measures [74,7474]		
Cancer risk (AYAHIV)	Updated RTI Cancer Survey		
Group education & sessions (AYAHIV)	Number & proportion of education sessions attended (dose)	PC tool, study database	12m, 24m, & 36m
One-on-one education (AYAHIV)	Number of women receiving each level of strategy (dose)		
HIV & cancer team trainings (provider)	Proportion who attended initial training sessions (dose)		
Network meetings (provider)	Number & proportion of meetings attended (dose)		
Clinical team knowledge, confidence in ability, & collaboration (providers)	Survey on skills, patient communication; AYAHIV stigma (modified Nyblade instrument[91]), & peer learning/coordination	Self-report	Baseline & annually
Diagnostic procedures by cancer type	Number of supplemental & diagnostic tests conducted	Clinic record	12m, 24m, & 36m
Treatment modality by cancer type	Chemotherapy sessions; surgery; type of radiation		

Abbreviations: HIV Human immunodeficiency virus, *KS* Kaposi sarcoma, *NHL* Non-Hodgkin's lymphoma, *CC* Cervical cancer, *PC* Peer Counselor, *AYAHIV* Adolescents and young adults living with HIV, *ART* Antiretroviral therapy, *RTI* Research Triangle Institute. Notes: [1]Among AYAHIV diagnosed with cancer; [2]NHL stage based on Lugano Classification, CC stage based on International Federation of Gynecology and Obstetrics, and KS stage based on AIDS Clinical Trial Group System

Analysis of Hypotheses

We will use an intent-to-treat approach to test the hypotheses (related to the dual primary and secondary endpoints) that AYAHIV in ARROW program, compared with those receiving one-time education, will have higher uptake of early diagnosis services, increased adherence to treatment, and improved outcomes.

For the facilities assigned to the intervention group in the early detection cohort, we will examine the effects at the individual level across the two randomization groups. Given the need to consider the influence of the cluster randomization, we will use generalized estimating equation (GEE) models to estimate the effect across the trial arms. If the Hausman assumption of correlation between the random and fixed effects is violated, then we will include fixed effects representing cluster identification [75]. For the cancer treatment cohort, we will generate summary statistics for the endpoints and test statistical significance. We will also conduct logistic regressions to identify key factors that predict adherence.

For both trials, we will adjust for baseline covariates, including sociodemographic factors, should the initial descriptive analyses suggest differences in the distribution of these factors across study arms.

We will also explore the use of propensity scores to control for systematic differences between AYAHIV in the two trial arms. In further analyses, we will compare differences in mediating outcomes across the randomized groups and examine the potential moderating roles of key individual behavioral and social factors hypothesized to influence adherence along the cancer care continuum (e.g., social support, stigma, self-efficacy), as shown in Figure 1. We will test the "dose" of the ARROW program received as a covariate in these models. In additional analysis, we will explore differences in the endpoints by age groups and type of cancer as appropriate. We will also assess whether knowledge, self-efficacy, social support, and stigma differ by age groups and among AYAHIV with and without cancer.

For measures where we have baseline, 12-month, 24-month, and 36-month data (e.g., self-efficacy and stigma), we will perform difference-in-difference analysis, which will allow for comparisons over time and across the study arms. To understand potential variation across HIV treatment facilities, we will conduct comparisons to analyze differences in AYAHIV mediating outcomes and study endpoints. Furthermore, to understand ARROW program's impact on providers, we will assess dose of the intervention (network session attendance) and change in knowledge, confidence in ability to care for AYAHIV, and peer collaboration.

Implementation Outcomes

For assessing the ARROW program, we will collect measures (as outlined in Table 3) from those receiving and implementing ARROW: 250 selected AYAHIV with follow-up data collection at the HIV treatment clinics and 250 AYAHIV at Cancer Diseases Hospital, 36 HIV providers, 12 oncology staff from Cancer Diseases Hospital, 10 Health Care Collaborative members, and all PCs. We will collect similar measures focused on the education campaign from those receiving the brochures in the one-time education campaign arm: 250 AYAHIV in the early detection cohort, 250 AYAHIV in the cancer treatment cohort, and 36 HIV providers.

Our measurement will include the four-item questions from the Acceptability of Intervention Measure (AIM), Feasibility of Intervention Measure (FIM), and Intervention Appropriateness Measure (IAM) [76]. Fidelity will be assessed using data collected in the PC tracking tool and Network meeting minutes. The fidelity measures described in Table 3 will be compiled annually, and summary statistics (e.g., proportion of sessions in which all content was delivered) will be generated to assess compliance with study protocols. Sustainability will be assessed using subscales of the Sustainment Measurement System Scale (SMSS) [77]. We will review the scores and fidelity measures and compare scores available for both the ARROW and one-time education arms to assess implementation success and draw lessons to improve and optimize the ARROW Program.

Table 3 Implementation outcomes measurement

Constructs	Measures	Stakeholder and Data	Frequency
Acceptability, feasibility, and appropriateness	AIM, FIM, and IAM four-item measures	AYAHIV, PCs, and provider (HIV and cancer) surveys	12-, 24-, and 36-month follow-up
Fidelity (group and one-on-one education, provider meetings, and education campaign)	All content is delivered or brochures are provided; meetings take place in the frequency and sequence planned	PCs tracking tool; Provider Network and Health Care Collaborative meeting minutes	12, 24, and 36 months
Sustainability	SMSS subscales specific to	PCs, providers, and	12 and 36

	strategies	administrators	months

Abbreviations: AIM Acceptability of intervention measure, *FIM* Feasibility of intervention measure, *IAM* Intervention appropriateness measure, *AYAHIV* Adolescents and young adults living with HIV, *PC* Peer Counselor, *HIV* Human immunodeficiency virus, *SMSS* Sustainment measurement system scale

We plan to conduct interviews and focus groups to identify underlying moderating factors associated with successful implementation of strategies along with facilitators and barriers to inform future scale-up activities. At 12 months, trained data collectors will interview PCs and providers as described for the quantitative measures. We will interview this group to seek feedback on their level of preparedness to implement the strategies, their assessment of the quality of the delivery, the level of responsiveness of the AYAHIV, whether they felt there were facilitators to deliver the strategies and potential barriers, and suggestions to address the barriers. We will also interview AYAHIV to seek feedback on the ARROW program and one-time education campaign.

At 36 months, at the end of the trials, we will conduct focus groups with PCs, AYAHIV, HIV providers, and oncology providers. These focus groups (7–10 participants) will explore topics related to the sustainability of the ARROW program and one-time education, drawing on the findings from the results of the SMSS survey. We will critically discuss interpretations of the data until they reach a consensus on the dominant themes and meanings. The findings will offer insights to improve the ARROW program and to understand perceptions of the one-time education campaign.

Cost-Effectiveness and Return-on-Investment Scenarios

We will assess the incremental cost-effectiveness of the ARROW Program compared with the one-time education campaign. As shown in Table 4, we will generate the cost of start-up activities to understand resources required to plan future implementation, the activity-based cost of strategies during the intervention trials, and estimated cost during scale-up. We will use a previously validated instrument, The Cost Assessment Tool, to collect resource use and cost information [78].

Our main goal is to estimate the implementation cost from the program perspective. We will estimate labor hours by prospectively tracking time spent by each project staff member, including PCs, on a predefined set of activities (individuals will report their time monthly) and use hourly wages to calculate cost. We will capture time spent by providers, administrators, and policy makers participating in the ARROW Network and Collaborative using minutes from the meetings. We will also document the expenditures on non-labor resources to produce education materials, hosting group education sessions, provider network meetings and cost of providing travel support. Using activity-based cost we will allocate separate costs for supporting early diagnosis services and treatment adherence.

Based on these cost estimates and the primary endpoints from the trial, we will conduct incremental cost-effectiveness analysis by generating cost per AYAHIV undergoing early detection services (physical exams for KS and NHL and screening for CC) and cost per AYAHIV with cancer completing recommended treatment modalities. Using standard economics methodology, we will explore economies of scale related to implementation costs that can be achieved during scale-up [78,79]. We will also assess the key drivers of the cost of the ARROW program.

Table 4 Cost data collection and analysis by phase

Phase	**Data Category**	**Purpose**	**Data Elements (examples)**
Pre-	Start-up costs	To assess cost of	Formalizing plans for the intervention;

implementation		planning to implement strategies	hiring staff; conducting training, readiness assessment, and strengthening processes
Intervention implementation (randomized trials)	Implementation activity-based cost data	To assess cost of implementing and maintaining interventions	Implementation activities: Delivering strategies; tracking outcomes, quality assurance, data collection, and evaluation Patient cost: Travel cost, time lost from work
	Resource use	To standardize cost	Labor hours (PCs and project staff), nonlabor resources
Future expansion	Scale-up cost	To estimate the cost of large-scale implementation	Fixed versus variable activity-based cost estimates of implementation strategies to project economies of scale

Abbreviations: PC Peer Counselor

Using the trial data on estimated shift in stage at diagnosis and treatment adherence rates, along with supplemental information on prevalence of KS, NHL, and CC and mortality by stage at diagnosis, we will estimate the projected difference in mortality between ARROW and one-time education for AYAHIV in Zambia. For CC screening, we will also estimate incremental change in mortality using a validated microsimulation model, as screening not only will identify CC at an early stage but also can prevent CC by treating precancerous lesions [81,82].

We will derive cost per life year saved (for all the three cancers combined), and our estimates will include both direct and indirect costs (patient time loss). The latter represents the opportunity cost of engaging in health services. We will assess whether the derived costs per life year saved are cost-effective or considered acceptable for implementation based on cost-effectiveness profiles of other strategies or interventions already implemented [83]. The estimated cost and effectiveness will be used to assess return on investment based on resources required to implement the ARROW program and the economic burden that will be reduced by avoiding premature mortality and treatments for adverse events related to KS, NHL, and CC for AYAHIV.

Furthermore, we will conduct policy simulations to assess the impact of scaling up ARROW and perform sensitivity analysis, varying the range of effectiveness and cost estimates, and generate potential best- and worst-case projections. We will create tornado and spider diagrams to display this uncertainty graphically to policy makers. This cost-effectiveness analysis will be complemented by a budget analysis, which will identify the financial outlays that will be required annually to implement the ARROW program at scale.

Results

Recruitment for both the early detection and cancer treatment cohorts is currently ongoing. Hypothesis-testing analysis, as well as cost-effectiveness and policy implication analysis, will be conducted. Twelve-month results will be available in early 2026.

Discussion

Limitations and Approaches to Minimize Bias

First, although cluster randomization reduces contamination across study arms, it increases the risk that AYAHIV in each arm may differ at baseline. The study sampling frame, based on the HIV registers, will allow us to assess baseline differences before facility randomization and adjust our sampling process with propensity score weights. Second, data could be missing because of

nonresponse and study attrition. The PCs will maintain regular contact with the AYAHIV, and we will employ rigorous field data collection practices, including training data collectors, developing protocols, and monitoring fidelity continually. Furthermore, we will address any missing data by including demographic covariates that will serve as proxies for dropout and conducting sensitivity analyses. Third, we anticipate provider turnover at the HIV treatment facilities and will conduct refresher trainings as needed throughout the trial period.

Impact and Policy Implications

The model tested in Zambia can serve as a blueprint for other Sub-Saharan African countries to ensure AYAHIV receive optimal services across the cancer care continuum. We will host consultation and policy forums to share findings and seek feedback on generalizability of the ARROW program to other Sub-Saharan settings. The ARROW program, if shown to be successful, will provide a framework for implementing integrated HIV and cancer services to improve outcomes and reduce mortality among AYAHIV.

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Authors' Contributions

SH, NC, ML, LN, MJ, CKW, MM, and SS were responsible for the concept and design of the manuscript. SB, PZ, RM, NC, DM, ML, CKM, MM, and SS were responsible for creating the data collection and analysis plan. SB, SH, and SS were responsible for drafting and revising the manuscript. All authors read and approved the final manuscript.

Consent for Publication

All authors have approved the final version of the manuscript.

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Ethics Approval and Consent to Participate

This study has received approval from the Population Council Ethics Committee and the ERES Coverage Institutional Review Board.

Conflicts of Interest

The authors report no conflicts of interest.

Abbreviations

AYA: adolescents and young adults
AYAHIV: AYA living with HIV
ART: antiretroviral therapy
KS: Kaposi Sarcoma
NHL: non-Hodgkin's lymphoma
CC: cervical cancer
NCCN: National Comprehensive Cancer Network
ARROW: AYAHIV Role-based Responsibilities for Oncology-focused Workforce

PC: peer counselor
ICC: interclass correlation coefficient
RTI: Research Triangle Institute
GEE: generalized estimating equation
AIM: Acceptability of Intervention Measure
FIM: Feasibility of Intervention Measure
IAM: Intervention Appropriateness Measure
SMSS: Sustainment Measurement System Scale

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Supplementary Files

Multimedia Appendixes

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