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Cohort profile: The comprehensive cervical cancer prevention in Tanzania (CONCEPT) study

Authors

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Abstract

Purpose

Cervical cancer is the cancer disease most women die from in Eastern Africa. To address the major burden of disease, the Comprehensive Cervical Cancer Project in Tanzania (CONCEPT) study was established in 2015, which involves the establishment of a prospective cohort. The cohort aims to investigate the natural history of HPV and cervical cancer in Tanzania and determine acquisition and persistence patterns of high-risk HPV– both type-specific and general – among HIV-positive and -negative women. Further, the influence of lifestyle and sexual/reproductive factors will be investigated.

Participants

Women aged 25-60 years were enrolled from cervical cancer screening clinics in Dar es Salaam and Moshi in Tanzania. Data were collected at baseline, at 14 months (1st follow-up) and at 28 months (2nd follow-up). Biological samples include cervical swabs for rapid HPV DNA-testing, cytology, Hybrid Capture 2, HPV-genotyping, and blood samples for HIV. Visual assessments included visual inspection with acetic acid and anthropometric measures included height and weight. Socio-demographic, lifestyle, reproductive, and sexual characteristics were collected by use of a standardised questionnaire.

Findings to date

4080 women were enrolled from august 2015 to May 2017. At baseline, 696 (17.2%) women were high-risk HPV-positive and among these 31.6% were HIV-positive. Further, 139 women (3.4%) had high grade squamous intraepithelial lesions. 3074 women (81%) attended the 1st follow-up. The majority attended after receiving a phone call reminder (35%) or participated from home via self-samples (41%). At 1st follow-up, 438 (14.4%) were high-risk HPV-positive and 30.4% of these were HIV-positive.

Future plans

We plan to integrate our data with a previous cross-sectional HPV study conducted in Tanzania to the increase power in our findings. Researchers interested in collaborating within this discipline are welcomed. This may involve extracting data from the project or jointly requesting further investigation from the cohort.

Registration

ClinicalTrials.gov: NCT02509702 (CONCEPT sub-study).

Strengths and limitations of this study

- This is a large-scale longitudinal cervical cancer study conducted in an HIV endemic population that aims to address a major cause of disease among East-African women, which so far has not received much focus within global health research.
- Women are followed over a long duration of time and with a large amount of data being collected by use of questionnaires and lab tests.
- It was difficult to get women to return for follow-up screenings. However, carefully designed tracing plans and dedicated home-visiting staff entailed that we managed to attain an 81% participation rate at 1st follow-up.
- Detailed HIV documentation was challenging to obtain, which has limited our ability and power in analyses involving HIV immunologic markers and treatment.

Introduction

Cervical cancer is a major cause of cancer-related mortality and morbidity globally, despite the disease being preventable. The highest prevalence is found among women aged 45-60 years[1], and the burden of disease

is disproportionally distributed among low- and middle-income countries (LMIC) and high-income countries (HIC) – LMICs account for 80% of cervical cancer cases worldwide. The global age-standardised incidence rate for cervical cancer is 14 per 100,000 women[2] while the incidence rate of cervical cancer is 42.7 per 100,0000 women in East Africa[3] and 54 per 100,000 women in Tanzania, specifically[4]. Major causes of the high burden of disease in resource-limited settings include unavailability of organised screening programmes; use of visual inspection with acetic acid (VIA) as standard screening method, which has shown to have low sensitivity[5, 6]; and low awareness of the disease and how to prevent it[7]. Further, there is limited longitudinal regional data of the natural history of the disease and the associated risk factors in these areas.

The aetiology of cervical cancer is multifactorial, however, persistent infection with a high-risk (HR) type of human papillomavirus (HPV) is a necessary cause for the disease. HPV is the most common sexually transmitted infection worldwide, and most sexually active individuals will acquire an HPV infection at some point in their lives[8]. Eighty to 90% of HPV infections clear spontaneously, however, 10-20% become persistent and can develop into pre-cancerous lesions and cervical cancer over time. There are different factors associated with HPV persistence, the two most significant ones are the type of HPV involved and immunodeficiency, hence HIV-positive women have increased risk of acquiring HPV[9] and for the infection to become persistent[10, 11]. HPV16 and 18 are the two most important types as these are associated with approximately 70% of all invasive cervical cancers worldwide[8]. Globally, the five most common types are HPV 16, 18, 52, 31, and 58[5, 6]. However, cross-sectional studies from Africa and systematic reviews on the global HPV burden indicate that the type-specific prevalence of HPV differs in Africa compared to other regions[2, 12, 13]. Further, sexual, reproductive, and lifestyle factors influence HPV acquisition and persistence, including smoking, high parity, number of sexual partners, long-term use of oral contraceptives, and co-infections with other sexually transmitted agents[14, 15]. However to date, there are no adequately powered longitudinal HPV studies among middle-aged women in East Africa that explore the association of HIV, immunological factors, reproductive, and lifestyle factors on HR HPV acquisition and persistence.

To our knowledge, only two HPV cohort studies and one large HPV cross-sectional study have been conducted in Africa, which explore the dynamics of HPV, HIV, and cervical cancer, namely (1) the HPV in Africa Research Partnership (HARP) HPV Study in Burkina Faso and Tanzania[16]; (2) the African Collaborative Center for Microbiome and Genomics Research (ACCME) study in Nigeria[17]; and (3) the Prevention of Cervical Cancer in Tanzania (PROTECT) study[18]. Other studies are nested in HPV vaccine trials[19-21]. These studies have provided some insight into the distribution of HPV among different African populations, however, they were either cross-sectional or conducted among adolescents' with inadequately powered HIV-positive women and a shorter duration of follow-up.

Initiatives to overcome cervical cancer in East Africa – and in Tanzania specifically – needs to be multifaceted and driven by evidence that accounts for the local factors that influence the burden of disease. Therefore, the Comprehensive Cervical Cancer Prevention in Tanzania (CONCEPT) study was launched in 2015 with an overall aim of improving prevention of cervical cancer in Tanzania (S1 Appendix). The CONCEPT study is an international collaborative study between Ocean Road Cancer Institute (ORCI), Kilimanjaro Christian Medical Centre (KCMC), University of Southern Denmark, and the Danish Cancer Society Research Center, and is to finish in December 2020. The CONCEPT study has several specific objectives that each focuses on different elements that are important in addressing the burden of cervical cancer, e.g. the (1) the natural history of HPV and how associated factors influence HR HPV occurrence, acquisition and persistence; (2) acceptability of an upcoming screening method for resource-limited settings, namely rapid HPV DNA testing[22] and how it performs compared to Hybrid Capture2 (HC2) and VIA for detection of cytologically diagnosed high-grade cervical lesions or cancer[6]; (3) how to ensure follow-up of HPV-positive women[23], and what motivates or prevents these women from returning to follow-up examinations[24, 25]. Introduction of HPV DNA testing in LMIC is challenging due to logistical problems inherent in these settings, however, HPV-based primary screening is a key method in future screening programmes across the world[26], and for it to be effectively established in resource-limited settings, local specific evidence is warranted. Therefore, in order to understand the natural history of HPV and cervical

neoplasia and specifically determine acquisition and persistence patterns of HR HPV– both type-specific and general – among HIV-positive and -negative women, a cohort of women with statistically adequate number of HIV-positives was established as part of the CONCEPT study. The aim of this article is to describe how this cohort was established and followed up, the profile of the cohort, and provide some characteristics of the cohort at enrolment and at the 1st follow-up.

Cohort description

Study design and study population

Women were enrolled from cervical cancer screening clinics at three study sites; (1) ORCI in Dar-es-Salaam as well as (2) KCMC and (3) Mawenzi regional referral hospital in the Kilimanjaro region. In Dar-es-Salaam, women from Ilala, Temeke, and Mwananyamala district were included while in the Kilimanjaro region, women originating from the urban and rural district of Moshi – including Hai and Rombo – were included. Originally, the study was designed as a double-site study (KCMC/ORCI), however, due to a slower-than-anticipated recruitment rate, a third study site (Mawenzi) was added six months into the enrolment period.

Women were eligible for inclusion if they were 25-60 years and attended a patient-initiated routine cervical cancer screening at one of the study sites. Women were excluded if they were pregnant, on their menstrual period, had a history of premalignant lesions of the cervix within the last 12 months, had previously been diagnosed with cervical cancer or had undergone abdominal hysterectomy. Following a detailed explanation of the study, all participants provided written informed consent. Fingerprints were used for illiterate participants. The CONCEPT study was approved by the Ethical Committee of the Tanzanian National Institute of Medical Research (NIMR/HQ/R.8a/Vol.IX/1955), and is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement (S2 Appendix).

Data were collected during the enrolment visit, at 14 months (1st follow-up), and at 28 months (2nd follow-up, ongoing). Healthcare providers working at the screening clinics enrolled participants and collected data following protocols developed specifically for the project. At inclusion, all participants were given a 14-months follow-up appointment written on an appointment card. If the women did not attend their follow-up visit within one month of their appointment, an active follow-up procedure was initiated. Firstly, non-attendees were contacted by phone and encouraged to attend (tracing method I). If the woman did not show up within two weeks of the phone call, the women had a home-visit by an outreach nurse who encouraged her to attend (tracing method II). If the woman still did not attend and consented to it, an outreach nurse visited her again and conducted the follow-up visit at home (tracing method III). Women, who participated in the first follow-up were appointed a second follow-up visit 28 months after initial recruitment. If the woman did not attend the 2nd follow-up, tracing method I and III were re-initiated.

Assessment of exposure

At inclusion, socio-demographic, lifestyle, reproductive, and sexual characteristics were collected during a personal interview using a modified version of a standardised questionnaire adopted from a previous study conducted in Tanzania[27] (S3 appendix). The questionnaire was hardcopy, developed in English while the interview was conducted in Kiswahili with direct translation. A Kiswahili version of the questionnaire was available to guide the interviewers. A detailed contact information form was filled out at enrolment and updated at follow-up. Participants were screened by trained healthcare providers according to the standard national cervical cancer screening prevention programme in Tanzania[28]. This entails a cost-free gynaecological examination with VIA, HIV-testing and HIV-counselling. Venous blood from the index finger was tested by use of a quick HIV-1/2 test (www.alere.com), and a supplementary quick HIV-1/2 test (Abbott Laboratories) was performed as confirmatory for positive results. Discordant results were further confirmed using Unigold (Trinity Biotech). Women who screened VIA-positive or were suspected of manifest cancer were managed on-site based on the National Cervical Cancer Service Delivery Guidelines.

This included treatment with cryotherapy or loop electrosurgical excision procedure (LEEP) for VIA-positives, and punch biopsy and referral for treatment at the oncology clinic at ORCI for cancer suspicions[28]. Further, weight and height were measured and registered on a hard-copy registration sheet together with the HIV- and VIA-result (Table 1).

Table 1. Overview of data collected in the CONCEPT cohort

	Measurements	Instrument	Storage and analysis
Baseline 17 Aug 2015 – 6 Jul 2017	**Biological samples** Provider-collected cervical swab for: • Rapid *care*HPV® DNA-testing	• Aryes spatula • Kept in *care*HPV collection medium	• Samples stored on-site in laboratories at room temperature • When 90 samples were available they were processed on-site on a *care*HPV machine • Results registered on *care*HPV sheet and stored on-site
	Provider-collected cervical swab for: • Cytology • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula • Kept in PreServCyt solution	• Samples stored on-site in laboratories at room temperature until enrolment had finished • Then the samples were sent to the Pathology Department at Lillebaelt Hospital, Denmark and processed on the ThinPrep5000 Autoloader Instrument, Hologic® for cytology • Remaining material of the samples were sent to the Section for Experimental Virology, Tubingen University, Germany and underwent HC2 DNA testing and genotyping using LiPaExtra • Cytology and HC2 and genotype results were sent to OUH, Denmark
	Venous blood from index finger for: • HIV-test	• Quick HIV-1/2 test	• Immediate results registered on registration form and stored on-site
	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• Immediate results registered on registration form and stored on-site
	Anthropometric measures • Weight • Height	• Scale and altitude meter	• Immediate results registered on registration form and stored on-site
	Personal interview • Socio-demographic factors • HIV treatment and CD4 count • Lifestyle factors • Sexual and reproductive factors	• Structured questionnaire	• Interviewed by nurse and stored on-site
14 - m	**Biological samples** Provider-collected cervical swab *or* self-collected swab for: • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula (provider-based) • Evalyn® brush (self-swab) • Kept in PreServCyt solution	• Self-swabs were conducted in the women's home (cf. tracing method III) and transferred to the study sites where they were stored with ThinPrep samples similarly to baseline until 1st follow-up had finished • Then the samples were sent to the

			Section for Experimental Virology, Tubingen University, Germany and underwent HC2 DNA testing and genotyping using LiPaExtra • HC2 and genotype results were sent to OUH, Denmark
	Venous blood from index finger for: • HIV-test (if negative at baseline)	• Quick HIV-1/2 test	• Immediate results registered on registration form and stored on-site • HIV-test was not conducted on women who participated from home (cf. tracing method III)
	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• Immediate results registered on registration form and stored on-site • Not conducted on women who participated from home (cf. tracing method III)
	Personal interview • HIV treatment and CD4 count • Sexual factors	• Structured questionnaire	• Interviewed by nurse at clinic or at home and stored on-site
28-months follow-up (2nd) *Ongoing*	**Biological samples** Provider-collected cervical swab *or* self-swab only for HPV-positive women: • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula (provider-based) • Evalyn® brush (self-swab) • Kept in PreServCyt solution	• *Same procedure as in 1st follow-up*
	Venous blood from index finger for: • HIV-test (if negative at 1st follow-up)	• Quick HIV-1/2 test	• *Same procedure as in 1st follow-up*
	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• *Same procedure as in 1st follow-up*
	Personal interview • HIV treatment and CD4 count • Sexual factors	• Structured questionnaire	• *Same procedure as in 1st follow-up*

Prior to the routine VIA examination, cervical swabs were taken using (1) an Aryes spatula for rapid *care*HPV test (www.qiagen.com), and (2) a ThinPrep® Pap Test Plastic Spatula for liquid-based cytology, HPV DNA testing and genotyping by use of Hybrid Capture2 (HC2) and LiPaExtra (Innogenetics, Gent, Belgium). The cervical samples for *care*HPV analysis were kept in a *care*HPV collection medium and stored at room temperature (max 25°C) in laboratories at ORCI or KCMC. Once 90 samples had been collected, they were analysed for HR HPV using a *care*HPV machine. A test was considered positive if one or more of

the following 13 HR HPV types were detected: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. The results were registered on a *care*HPV results sheet (Table 1).

The samples for HC2 testing and cytology were kept in a PreServCyt solution (Hologic, Inc. 250 Campus Drive Marlborough, MA 01752 USA) and stored at room temperature in laboratories at ORCI and KCMC. Once enrolment had finished, the PreServCyt vials were sent to the Department of Pathology at Lillebaelt Hospital, Vejle, Denmark and processed at the ThinPrep5000 Autoloader Instrument, Hologic® according to manufactures instruction and stained with ThinPrep Stain®. The slides were scanned by the Thin Prep Imaging System® with selection of 22 Fields of view which was reviewed by cytotechnologist in review scopes. The specimens were evaluated for adequacy and for abnormal cells. If abnormal cells were detected, the slides were consulted with a gynae-pathologist who made the final diagnosis. The specimens were diagnosed according to the Bethesda Nomenclature for System for Cervical Cytology 2014[29] into following categories: Negative for intra epithelial lesion (NILM), Atypical Squamous Cell of Undetermined Significance (ASCUS), Atypical Squamous Cell in which High grade squamous intraepithelial lesion cannot be excluded (ASCH), Low grade Squamous Intraepithelial Lesion (LSIL), High grade Squamous Intraepithelial Lesion (HSIL), Atypical Glandular Cell (AGC), Adenocarcinoma In Situ(AIS), and Adenocarcinoma. The remaining material of the PreServCyt vials were sent to the Section for Experimental Virology, Tubingen University, Germany for HPV DNA testing and genotyping. HPV DNA testing was done using HC2 DNA test (www.qiagen.com) with a high-risk cocktail probe. A test was considered positive if one or more of the following 13 HR HPV types were found: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68. A threshold of 1.0pg HPVDNA/ml, which corresponds to 1.0 relative light unit coefficient, was used, as recommended by United States Food and Drug Authority. HPV-positive samples were genotyped using LiPaExtra, which can detect 28 HPV types, 18 HR risk types (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and 10 low risk types (HPV 6, 11, 40, 43, 44, 54, 69, 70, 71, 74)[30].

Outcome measures

Women who attended their follow-up appointment at the screening clinics were HIV-tested (if negative at baseline), had a cervical swab collected with a ThinPrep® Pap Test Plastic Spatula for HPV DNA testing by use of HC2 and genotyping using LiPaExtra and underwent VIA (Table 1). Further, sexual and reproductive characteristics were updated by use of a structured questionnaire (S4 Appendix). Women who did not attend their follow-up appointment at the clinic but consented to having a home-visit appointment (cf. tracing method III) responded to the questionnaire and had cervical specimens collected by use of an Evalyn self-sampling/self-swab device (www.roversmedicaldevices.com). The samples were transferred to laboratories at ORCI and KCMC where they were kept in a PreServCyt solution and stored at room temperature.

Data management

Questionnaires, registrations forms, contact forms, and *care*HPV result sheets were stored in different cabinets in locked offices at KCMC and ORCI, after which they were double entered into EpiData by data clerks. Together with lab results these data were sent to the Research unit for Gynaecology & Obstetrics, Odense University Hospital (OUH), Odense, Denmark where they were merged and constructed into a baseline database. Data with invalid IDs or no data registered were excluded upon creation of the database. Similarly to baseline, follow-up data were sent to OUH after which it was merged with the baseline database. Follow-up IDs that could not match a baseline ID were excluded.

Patient and public involvement

Study participants were not involved in the design or recruitment of the study.

Findings to date

Baseline findings

A total of 4080 women were enrolled into the CONCEPT study. After inclusion, 37 study participants were excluded leaving the total cohort to consist of 4043 women (fig 1). The baseline distribution of the socio-

demographic is presented in Table 2. A total of 718 women (17.8%) were HIV-positive and the majority of these were 35-39 years old (22.9%) while the majority of HIV-negative women were 40-44 years old (19.2%). Among the HIV-positives, 49.7% were married (n=356) whilst 73.6% of HIV-negatives were married (n=2434). Most of both HIV-positive (70.4%; n=504) and HIV-negative women (64.1%; n=2127) had completed primary school. More HIV-negative women (87.0%; n=2879) reported to have had sex within the last 12 months compared to HIV-positive women (72.7%; n=520), while more HIV-positives (26.2%) than HIV-negatives (9.8%) reported to have had used condoms at every intercourse. In relation to number of lifetime partners, 71.9% of HIV-positives reported having more than one lifetime partner whilst the corresponding number for HIV-negative women was 61.0%. The CD4 count for HIV-positive women were as follows: 8.6% (n=62) reported having a CD4 count ≤199; 30.5% (n=219) had a CD4 ranging from 200-499; and 48.9% (n=347) had a CD4 count ≥500. Further, 12.5% (n=90) of the HIV-positives did not report the CD4 count.

Table 2: Selected sociodemographic, lifestyle, sexual and reproductive characteristics of the cohort at baseline and 1st follow-up stratified according to HIV-status

	COHORT PROFILE AT BASELINE						COHORT PROFILE AT 1ST FOLLOW-UP					
	Total (n=4043)		HIV-positive (n=718; 18%)		HIV-negative (n=3325, 82%)		Total (n=3074)		HIV-positive* (n=552; 18%)		HIV-negative* (n=2522; 82%)	
	N	%	N	%	N	%	N	%	N	%	N	%
Age												
25-29	527	13.0	43	6.0	484	14.6	344	11.2	26	4.7	318	12.6
30-34	599	14.8	78	10.9	521	15.7	432	14.1	61	11.1	371	14.7
35-39	744	18.4	164	22.9	580	17.5	547	17.8	121	21.9	426	16.9
40-44	787	19.5	149	20.8	638	19.2	634	20.6	115	20.8	519	20.6
45-49	667	16.5	138	19.2	529	15.9	522	17.0	112	20.3	410	16.7
50-60	716	17.7	145	20.2	571	17.2	595	19.4	117	21.2	478	18.9
Missing	3	0.1	1	0.14	2	0.06	-	-	-	-	-	-
Marital status												
Married	2790	69.0	356	49.7	2434	73.6	2159	70.2	288	52.2	1871	74.2
Cohabiting	58	1.4	14	2.0	44	1.3	44	1.4	11	2.0	33	1.3
Single	487	12.0	110	15.4	377	11.4	335	10.9	76	13.8	259	10.3
Divorced/widow	687	17.0	236	33.0	451	13.6	527	17.1	176	31.9	351	13.9
Missing	21	0.5	2	0.28	19	0.57	9	0.3	1	0.2	8	0.3
BMI												
Underweight	96	2.4	27	3.9	69	2.1	73	2.4	21	3.8	52	2.1
Normal	1149	28.4	269	38.5	880	27.3	839	27.3	199	36.1	640	25.4
Overweight	2190	54.2	334	47.8	1856	57.6	1695	55.1	259	46.9	1436	56.9
Obese	486	12.0	69	9.9	417	12.9	406	13.2	59	10.7	347	13.8
Missing	122	3.0	19	2.15	103	3.1	61	2.0	14	2.5	47	1.9
Education level												

No formal education	126	3.1		32	4.5		94	2.8		89	2.9		23	4.2		66	2.6
Primary	2631	65.1		504	70.4		2127	64.1		2027	65.9		381	69.0		2027	65.3
Secondary	882	21.8		146	20.4		736	22.2		672	21.9		123	22.3		672	21.8
College	396	9.8		34	4.7		362	10.9		280	9.1		23	4.2		280	10.2
Missing	8	0.2		2	0.28		6	0.18		6	0.2		2	0.4		6	0.7
Religion																	
Christian	2708	67.0		505	70.6		2203	66.8		2064	67.1		391	70.8		1673	66.3
Muslim	1289	31.9		206	28.8		1083	32.8		978	31.8		155	28.1		823	32.6
Other	16	0.4		4	0.6		12	0.4		13	0.4		4	0.7		9	0.4
Missing	30	0.7		3	0.42		27	0.81		19	0.6		2	0.7		17	0.6
No of living children																	
0	35	0.9		5	0.7		30	0.9		22	0.7		4	0.7		18	0.7
1-2	1506	37.2		295	41.8		1211	37.5		1112	36.2		219	39.7		893	35.4
3	901	22.3		180	25.5		721	22.3		729	23.7		141	25.5		588	23.2
4-6	1135	28.1		183	25.9		952	29.5		900	29.3		150	27.2		750	29.7
>7	139	3.4		19	2.7		120	3.7		99	3.2		12	2.2		87	3.5
Never been pregnant	221	5.5		24	3.4		197	6.1		144	4.7		16	2.9		128	5.1
Missing	106	2.6		12	1.67		94	2.83		68	2.2		10	1.8		58	2.3
Years living with partner																	
0-1	166	4.1		21	3.0		145	4.4		102	3.3		18	3.3		84	3.3
2-4	517	12.8		112	15.9		405	12.4		355	11.6		74	13.4		281	11.4
5-9	723	17.9		143	20.3		580	17.8		515	16.8		106	19.2		409	16.2
10-14	648	16.0		125	17.7		523	16.0		502	16.3		97	17.6		405	16.1
15-19	546	13.5		104	14.8		442	13.6		443	14.4		85	15.4		358	14.2
>20	1203	29.8		162	23.0		1041	31.9		993	32.2		137	24.8		856	33.9
Single with no regular partner	163	4.0		38	5.4		125	3.8		118	3.8		27	4.9		91	3.6
Missing	77	1.9		13	1.81		64	1.92		46	1.5		8	1.5		38	1.5
Sex in last 1 year																	
Yes	3399	84.1		520	72.7		2879	87.0		2583	84.0		404	73.2		2179	86.4
No	610	15.1		195	27.3		415	12.5		478	15.6		146	26.5		332	13.2
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	20	0.5		3	0.42		17	0.51		8	0.3		2	0.4		6	0.2
Condom use within last 12 months																	
No sex within last 12 months	610	15.1		195	27.3		415	12.6		478	15.6		146	26.5		332	13.2
At every intercourse	509	12.6		187	26.2		322	9.8		381	12.4		139	25.2		242	9.6
Rarely	204	5.0		29	4.1		175	5.3		146	4.8		25	4.5		121	4.8
No condom use	2678	66.2		303	42.4		2375	71.9		2052	66.8		239	43,3		1813	71.9
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	28	0.7		4	0.56		24	0.72		12	0.4		3	0.5		9	0.4
Number of lifetime partners																	
1	1476	36.5		197	28.1		1279	39.0		1129	36.7		158	28.6		971	38.5
2	1053	26.0		194	27.7		859	26.2		819	26.6		155	28.1		664	26.3
3	709	17.5		147	21.0		562	17.1		516	16.8		101	18.2		415	16.5
4	284	7.0		60	8.6		224	6.8		221	7.2		46	8.3		175	6.8
5-8	329	8.1		65	9.3		264	8.1		255	8.3		49	8.9		206	8.2
>9	113	2.8		38	5.4		75	2.3		89	2.9		33	6.0		56	2.2
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	65	1.6		17	2.4		48	1.4		40	1.3		10	1.8		30	1.2

**According to HIV-status at baseline*

Among the 4043 participants at baseline, the cervical sample was insufficient for HPV analysis in 396 women (9.8%) leaving 3667 women eligible for analysis of HPV-positivity. Further, 27 women (0.5%) did not have any cervical cytology, leaving 4116 women available for cytological analysis of cervical lesions. All 4043 women were either tested for HIV or had previously tested HIV-positive. At baseline, 696 women (17.2%) tested HR HPV-positive by HC2. The cytology showed that overall 3.4% (n=139) had HSIL+ whilst 8.1% (n=329) of women had LSIL.

1st follow-up findings

A total of 3805 women (94%) were eligible for 1st follow-up – 238 women (6%) were ineligible due to becoming pregnant, having moved, having had a hysterectomy or having become sick or died (fig 1). Of the 3805 women, 3074 women (81%) attended the first follow-up visit approximately 14th months after enrolment. However, among the attendees only 500 (16%) attended within in 30 days of their scheduled appointment date and without being traced for follow-up. A total of 1088 (35%) attended the clinic after a phone call reminder (tracing method I), 62 women (2%) attended the clinic after a nurse home-visit (tracing method II), whilst 1253 women (41%) were followed up at home and had specimens collected using self-sampling device (tracing method III). A total of 731 women (19%) were lost to follow-up (fig 1).

(Fig 1: Flow chart of enrolment and follow-up of CONCEPT cohort)

The women who participated in the 1st follow-up were very similar to those who did not attend when looking at socio-demographic factors (table 2). However, overall fewer women were HR HPV-positive at follow-up compared to baseline (14.8% vs. 17.2%), and fewer HIV-positive women were HR HPV-positive at follow-up compared to baseline (24.1% vs. 33.7%) (table 3).

Table 3. High-risk HPV, HIV, and cytology results at baseline and 1st follow-up

Baseline		First follow up

	Total (N=4043)				Total (N=3074)		
HPV	**n**	**%**	**(95% CI)**		**n**	**%**	**(95% CI)**
Positive	696	17.2	(0.16-0.18)		438	14.3	(0.13-0.16)
Negative	2951	73	(0.72-0.74)		2595	84.4	(0.83-0.86)
Missing	396	9.8	(0.09-0.1)		41	1.3	(0.01-0.02)
HIV							
Positive	718	17.8	(0.17-0.19)		552	18	(0.17-0.2)
Negative	3325	82.2	(0.81-0.83)		2522	82	(0.80-0.83)
Cytology							
HSIL	139	3.4	(0.03-0.04)				
LSIL	329	8.1	(0.07-0.09)				
Negative	3548	87.8	(0.87-0.89)				
Missing	27	0.7	(0.00-0.01)				

Strengths and Limitations

This is a large-scale longitudinal cervical cancer study conducted in an HIV endemic population that aims to address a major cause of disease among East-African women, which so far has not received much focus within global health research. Women are followed over a long duration of time and with a large amount of data being collected by use of questionnaires and lab tests. Given the nature of our study a significant attrition rate was expected. However, with the carefully designed tracing plans and dedicated home-visiting staff we managed to attain an 81% participation rate at 1st follow-up. As women were enrolled during a patient-initiated screening at screening clinics, detailed HIV documentation was challenging to obtain as Care and Treatment Clinic (CTC) cards were poorly documented or had not been brought to the screening. Despite the nurses calling these women after enrolment to retrieve the information, it was not provided by many HIV-positive participants. This has led to a certain amount of missing values for a few variables and have limited our ability and power in analyses involving HIV immunologic markers and treatment.

Future plans

Based on our large-scale data of both HPV infection in general and type specific characterised by the women's HIV-status, we plan to integrate this data with a previous cross-sectional HPV study (PROTECT Study) conducted in this population as this can increase power in our findings. As we have already established a large cohort of participants, we foresee a potential to further characterise the natural history of HPV, the HPV burden and HPV-related disease and establish potential risk factors over a longer course of time. Further, we also foresee the possibility of linking our evidence with other groups in this population including males, adolescents, and pregnant women. This may provide additional information on the similarities of epidemiological burden among these group and delineate differences in the correlations of HPV and HPV-related disease across these different groups.

Collaboration

Researchers interested in collaboration in this discipline especially in East and Central Africa are welcomed. This may be in extracting data from the project, jointly requesting further investigation from the cohort.

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Contributers

JM, RM, VR, and SKK designed the CONCEPT study. JM, RM, RV, SKK, JK, PS, CK, BM, and DSL were involved in collecting data for the study. CW, SKK, VR, BM, and DSL, were involved in data analysis and interpretation. CW, BM, DSL contributed to the conception of this article, and CW, BM, DSL, PS, JK, CK, VR, JM, SKK, and RM were involved in the manuscript writing and revision. All authors read and approved the final manuscript.

Data sharing statement

Data collected for the CONCEPT cohort study are available upon request. Individual participant data will de-identified. Additional available data include the CONCEPT eligibility and informed consent form, the CONCEPT contact information form, the protocol for how to deliver HPV-positive results to participants, the protocol for how to trace non-attendants. Data will be made available upon request by contacting the first or last author of this study by email at barikimchome@gmail.com/dsondergaard@health.sdu.dk, who will then seek approval by the primary investigator in the CONCEPT project, Julius D. Mwaiselage.

Supplementary material

S1 appendix	Original protocol for CONCEPT study
S2 appendix	STROBE checklist
S3 appendix	CONCEPT baseline questionnaire
S4 appendix	CONCEPT 1st follow-up questionnaire

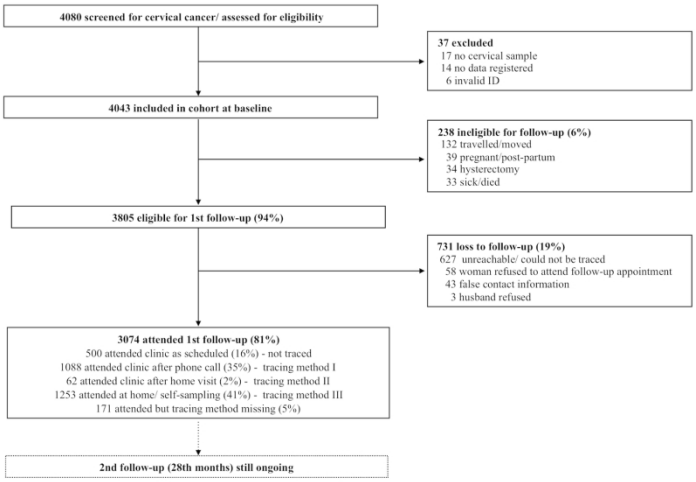
Abbreviations

ACCME	African Collaborative Center for Microbiome and Genomics Research
AGC	Atypical glandular cell
AIS	Adenocarcinoma in situ
ASCUS	Atypical squamous cell of undetermined significance
ASCH	Atypical squamous cell in which High grade squamous intraepithelial lesion cannot be excluded
CTC	Care and treatment clinic
CONCEPT	Comprehensive Cervical Cancer Prevention in Tanzania
Danida	Danish International Development Agency
HARP	HPV in Africa Research Partnership
HC2	Hybrid Capture 2
HIC	High-income countries
HIV	Human immuno-deficiency virus
HPV	Human papilloma virus
HSIL	High grade squamous intraepithelial lesion
KCMC	Kilimanjaro Christian Medical Centre
LEEP	Loop electrosurgical procedure
LMIC	Low- and middle-income countries
LSIL	Low grade squamous intraepithelial lesion
NILM	Negative for intra epithelial lesion
PROTECT	Prevention of Cervical Cancer in Tanzania
ORCI	Ocean Road Cancer Institute

References

1. World Health Organisation: **Improving data for decision-making: a toolkit for cervical cancer prevention and control programmes**. In. Geneva: World Health Organization; 2018.
2. Serrano B, Brotons M, Bosch FX, Bruni L: **Epidemiology and burden of HPV-related disease**. *Best Pract Res Clin Obstet Gynaecol* 2018, **47**:14-26.
3. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A: **Global Cancer in Women: Burden and Trends**. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2017, **26**(4):444-457.
4. Bruni LB-RL AG, Serrano B: **Human Papillomavirus and Related Diseases in Tanzania.Summary Report.** *ICO Information Centre on HPV and Cancer (HPVInformation Centre)* 2016, **15**.
5. Dartell MA, Rasch V, Iftner T, Kahesa C, Mwaiselage JD, Junge J, Gernow A, Ejlersen SF, Munk C, Kjaer SK: **Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative Tanzanian women**. *International journal of cancer* 2014, **135**(4):896-904.
6. Katanga J, Kjaer SK, Manongi R, Wu CS, Iftner T, Waldstrom M, Pembe AB, Mwaiselage J, Rasch V: **Performance of careHPV, hybrid capture 2 and visual inspection with acetic acid for detection of high-grade cervical lesion in Tanzania: A cross-sectional study**. *PloS one* 2019, **14**(6):e0218559.
7. Gard AC, Soliman AS, Ngoma T, Mwaiselage J, Kahesa C, Chamberlain RM, Harlow SD: **Most women diagnosed with cervical cancer by a visual screening program in Tanzania completed treatment: evidence from a retrospective cohort study**. *BMC public health* 2014, **14**:910.
8. Bruni L, Diaz M, Castellsague X, Ferrer E, Bosch FX, de Sanjose S: **Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings**. *J Infect Dis* 2010, **202**(12):1789-1799.
9. Nowak RG, Gravitt PE, Morrison CS, Gange SJ, Kwok C, Oliver AE, Howard R, Van der Pol B, Salata RA, Padian NS *et al*: **Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe**. *J Infect Dis* 2011, **203**(8):1182-1191.
10. Dames DN, Blackman E, Butler R, Taioli E, Eckstein S, Devarajan K, Griffith-Bowe A, Gomez P, Ragin C: **High-risk cervical human papillomavirus infections among human immunodeficiency virus-positive women in the Bahamas**. *PloS one* 2014, **9**(1):e85429.
11. Looker KJ, Ronn MM, Brock PM, Brisson M, Drolet M, Mayaud P, Boily MC: **Evidence of synergistic relationships between HIV and Human Papillomavirus (HPV): systematic reviews and meta-analyses of longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status**. *Journal of the International AIDS Society* 2018, **21**(6):e25110.
12. Akarolo-Anthony SN, Famooto AO, Dareng EO, Olaniyan OB, Offiong R, Wheeler CM, Adebamowo CA: **Age-specific prevalence of human papilloma virus infection among Nigerian women**. *BMC public health* 2014, **14**:656.
13. Guan P, Howell-Jones R, Li N, Bruni L, de Sanjose S, Franceschi S, Clifford GM: **Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer**. *International journal of cancer* 2012, **131**(10):2349-2359.
14. WHO (2019). World Health Organization. Human papillomavirus (HPV) and cervical cancer [Internet] Available from .https://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer
15. Bosch FX, Munoz N: **The viral etiology of cervical cancer**. *Virus research* 2002, **89**(2):183-190.
16. Kelly HA, Ngou J, Chikandiwa A, Sawadogo B, Gilham C, Omar T, Lompo O, Doutre S, Meda N, Weiss HA *et al*: **Associations of Human Papillomavirus (HPV) genotypes with high-grade cervical neoplasia (CIN2+) in a cohort of women living with HIV in Burkina Faso and South Africa**. *PloS one* 2017, **12**(3):e0174117.
17. Adebamowo SN, Dareng EO, Famooto AO, Offiong R, Olaniyan O, Obende K, Adebayo A, Ologun S, Alabi B, Achara P *et al*: **Cohort Profile: African Collaborative Center for Microbiome and Genomics Research's (ACCME's) Human Papillomavirus (HPV) and Cervical Cancer Study**. *International journal of epidemiology* 2017, **46**(6):1745-1745j.
18. Dartell M, Rasch V, Kahesa C, Mwaiselage J, Ngoma T, Junge J, Gernow A, Ejlersen SF, Munk C, Iftner T *et al*: **Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study**. *Sexually transmitted diseases* 2012, **39**(3):201-208.

19. Watson-Jones D, Baisley K, Brown J, Kavishe B, Andreasen A, Changalucha J, Mayaud P, Kapiga S, Gumodoka B, Hayes RJ *et al*: **High prevalence and incidence of human papillomavirus in a cohort of healthy young African female subjects**. *Sexually transmitted infections* 2013, **89**(5):358-365.
20. Houlihan CF, Baisley K, Bravo IG, Kapiga S, de Sanjose S, Changalucha J, Ross DA, Hayes RJ, Watson-Jones D: **Rapid acquisition of HPV around the time of sexual debut in adolescent girls in Tanzania**. *Int J Epidemiol* 2016, **45**(3):762-773.
21. Baisley KJ, Andreasen A, Irani J, Nnko S, Changalucha J, Crucitti T, Francis S, Holm Hansen C, Hayes RJ, Buve A *et al*: **HPV prevalence around the time of sexual debut in adolescent girls in Tanzania**. *Sex Transm Infect* 2019.
22. Tsu VD, Njama-Meya D, Lim J, Murray M, de Sanjose S: **Opportunities and challenges for introducing HPV testing for cervical cancer screening in sub-Saharan Africa**. *Preventive medicine* 2018, **114**:205-208.
23. Linde DS, Andersen MS, Mwaiselage JD, Manongi R, Kjaer SK, Rasch V: **Text messages to increase attendance to follow-up cervical cancer screening appointments among HPV-positive Tanzanian women (Connected2Care): study protocol for a randomised controlled trial**. *Trials* 2017, **18**(1):555.
24. Linde DS, Rasch V, Mwaiselage JD, Gammeltoft TM: **Competing needs: a qualitative study of cervical cancer screening attendance among HPV-positive women in Tanzania**. *BMJ open* 2019, **9**(2):e024011.
25. Linde DS AM, Mwaiselage JD, Manongi R, Kjaer SK, Rasch V: **One-way text messages versus no text messages on attendance to follow-up cervical cancer screening among HPV-positive Tanzanian Women (Connected2Care): a parallel-group randomized controlled trial**. *JMIR Preprints* 15/08/2019:15863.
26. Koliopoulos G, Nyaga VN, Santesso N, Bryant A, Martin-Hirsch PP, Mustafa RA, Schunemann H, Paraskevaidis E, Arbyn M: **Cytology versus HPV testing for cervical cancer screening in the general population**. *The Cochrane database of systematic reviews* 2017, **8**:Cd008587.
27. Dartell M, Rasch V, Munk C, Kahesa C, Mwaiselage J, Iftner T, Kjaer SK: **Risk factors for high-risk human papillomavirus detection among HIV-negative and HIV-positive women from Tanzania**. *Sexually transmitted diseases* 2013, **40**(9):737-743.
28. **Cervical Cancer Prevention Guidelines for Low-Resource Settings** [http://reprolineplus.org/system/files/resources/CeCaPfullmanual.pdf]
29. Nayar R, Wilbur DC: **The Pap Test and Bethesda 2014. "The reports of my demise have been greatly exaggerated." (after a quotation from Mark Twain)**. *Acta Cytol* 2015, **59**(2):121-132.
30. Xu L, Padalko E, Ostrbenk A, Poljak M, Arbyn M: **Clinical Evaluation of INNO-LiPA HPV Genotyping EXTRA II Assay Using the VALGENT Framework**. *Int J Mol Sci* 2018, **19**(9).



Flow chart

190x134mm (300 x 300 DPI)

Appendix A: Project Description

Comprehensive Cervical Cancer Prevention in Tanzania (CONCEPT)

1. Project Summary

The natural history of Human papillomavirus (HPV) in sub-Saharan Africa is not yet fully understood. As persistent HPV infection is a necessary factor in development of cervical cancer – a major health problem in sub-Saharan Africa - information about how HIV together with other risk factors interacts with HPV acquisitionand HPV persistence/clearance is warranted. Additionally, concern prevails about the quality of cervical cancer preventive strategies in sub-Saharan Africa. Against this background the project aims to provide a better understanding of the natural history of HPV with a view to HIV status, to measure the impact of a novel and simple screening method based on *Care*HPV testing and to assess how continuity of care among women who are tested HPV positive can be improved. The study will be linked up with the existing cervical cancer screening program at Ocean Road Cancer Institute (ORCI) and Kilimanjaro Christian Medical Centre (KCMC); and will include 4000 women who are attending screening service or HIV care and treatment. HPV acquisition and persistence/clearance patterns as well as the absolute risk of severe cervical precancerous lesions will be determined through a follow up study lasting 28 months. The test performance of *Care*HPV testing, liquid-based cytology and VIA will be described and the operating characteristics of the three screening methods will be assessed according to HIV status. Finally, the impact of a mobile phone intervention and a patient navigation model will be assessed and compared according to the proportion of HPV positive women who return for follow-up examinations. Additionally, the project will implement a research capacity building component focusing on transfer of knowledge and technology as well as training of PhD students. The activities will be carried out as five sub-studies: i) HPV acquisition pattern; ii) HPV persistence/clearance pattern; iii) Test performance of *Care*HPVtesting, liquid-based cytology and VIA; iv) Continuity of care among screened positive women and v) research capacity building as well as transfer of knowledge and technology

2. Objectives

With the overall aim of substantially improving cervical cancer prevention in Tanzania and thereby reduce mortality, the CONCEPT project focuses onthe natural history of human papillomavirus (HPV), which is the most important risk factor for cervical cancer.

HPV can take the form of being either a transient infection, that relatively rapidly is cleared by the host immune system or it can becomea persistent infection that may progress to high-grade cervical lesions or cervical cancer**(Fig. 1)**.In spite of the fact that cervical cancer is the most common malignancy among women in Sub-Saharan Africa (1), little is known about the distribution of HPV types, risk factors of incidence and patterns of persistence for different HPV types. The proposed project will address this lack of knowledge and provide new information about the natural history of HPV and consequences of HPV infection among HIV positive and HIV negative women.In addition, there is concern about the performance of the screening approaches applied in many sub-Saharan African countries and information on the quality of novel, affordable screening approaches that will perform well in remote areas iswarranted. Finally, in many sub-Saharan African settingsworries prevail about lack of continuity of care among women who are diagnosed with precancerous lesionsand therefor relevant treatment is not always offered. The proposed project will address these shortcomings in cervical cancer prevention. The researchwill build on the resultspreviously obtained by our research team(2-6) and will be innovative in the way that it through a comprehensive approach will use thenatural history of HPV to identify opportunities to strengthening and further develop the existing screening program in Tanzania, with a particular view to the importance of HIV positivity. In addition, with the aim to bridge the gap in continuity of care among women diagnosed with precancerous lesions,the project will develop and test a reliable and sustainable communication system through a multidisciplinary approach, involving community education, social mobilization and use of cell-phones. Thus the proposed study has the potential to produce results with immediate public health impact.

The specific objectives of the project are:

1. To assess acquisition patterns and incidence of HPV infection with a specific focus on differences in HPV acquisition, distribution of HPV types and risk factors among HIV positive and HIV negative women

2. To assess persistence of high-risk HPV infection with a specific focus on whether there are differences in HPV persistence in relation to specific HPV types and differences in risk factors for HPV persistence among HIV positive and HIV negative women. In addition, it is the aim to examine the absolute risk of HSIL or worse in relation to both one time HPV positivity and HPV persistence while taking HIV status into account

3. To evaluate the performance ofSelf collected *Care*HPV testing, health provider collected HPV test, Pap smear (liquid-based cytology) and visual inspection with acetic acid (VIA) for detection of cervical precancerous lesions with a special view to test performance among HIV positive and HIV negative women.

4. To evaluate and compare two different interventions aiming at ensuring continuity of care among women who are tested HPV positive in terms of effect and costs, and to describe barriers for not adhering to the scheduled follow-up

5. To enhance research capacity and transfer of knowledge and technologythrough the training of PhD students and the involvement of a post-doctoral fellow

3. Project's methodology

Based on the experience and success of our previous study of HPV prevalence in Tanzanian women, the present study will be linked up with the existing cervical cancer screening program in Dar es Salaam and Kilimanjaro Region. To make sure that we will include enough HIV positive women into the study, we will oversample HIV positive women. This will be done through enrolment of women attending HIV care and treatment in the two study areas.A total of 4000 women will be enrolled at baseline in the study -3500 women from the two screening settings and 500 HIV positive women from two HIV care and treatment clinics. Based on our previous experience, amongthe 3500 women recruited from the screening settings, around 700 will be high-risk (HR)-HPV positive and nearly 350 women will be HIV positive(2). Among the 500 HIV positive women recruited from the HIV clinics, an estimated 250 women will beHPV positive(2). Hence, the total study sample of 4000 women will include an estimated 950 HPV positive and 850 HIV positive women.A power calculation was based on McNemars test in the situation where we compare two diagnostic tests (1: standard test (VIA)vs 2:new test (*Care*HPV)) where the outcome is sensitivity S_1 and S_2, respectively.Based on our previous studies in Tanzania (4) it is estimated that 180-200 women will have precancerous lesions at baseline (~true positive), and we assume a significance level of 5% and that the sensitivity of the standard test is S_1=30%. We will then with 80% power be able to detect a significant difference if the sensitivity of the new test is at least S_2=44%. As we anticipate *Care*HPV testing to have a much higher sensitivity, we will have sufficient power in the present study

An overview of the study design is outlined in **Fig. 2.** In principle the study comprises a baseline visit and 2 follow-up visits:

*At **baseline*** we will collect on all participating women a cervical sample for *Care*HPV testing, a novel and simple quick test for detection of HPV.We will also obtaina liquid-based cervical swab (ThinPrep) for cytology examination (subsequently prepared and diagnosedin Denmark), high-risk Hybrid Capture (HC2) testing (in Germany), and genotyping (PCR-based HPV testing in Germany). Following this, VIA will be done with 5% acetic acid. The Tanzanian staff will receive training (re-training) in sample collection and VIA before start of the study by national trainers according to IARC guidelines. In case of a positive cytology (HSIL or worse) the woman will be called in and will be treated according to the cervical cancer screening standard of care methods in Tanzania. Similarly, all VIA positive women will be treated according to the cervical cancer screening standard of care methods in Tanzania.Information on socio-economic characteristics, lifestyle factors and reproductive history will be recorded through a personal

interview, and blood samples for HIV testing will be obtained. Before the initiation of the study, the staff in Tanzania will receive training in *Care*HPV testing.The C*are*HPV (including currently known HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) will be tested within 14 days in Tanzania. At the ***first follow-up*****,** taking place 14 months after inclusion,a randomly selected sample of 500 women will be trained on self-collection of a cervical swab for HPV testing. Thereafter another cervical swab (ThinPrep) will be collected (on all study subjects in the 1st follow-up) by a trained health provider. At the ***second follow-up*****,** taking place 26 months after inclusion, a cervical swab (ThinPrep) will be obtained from each woman. Women who do not return to the clinic for first and second follow-up will be traced and visited at home and invited to attend the clinic for screening. If they do not wish to re-attend, they will be offered screening through a self-collected HPV sample.We anticipate a response rate in the 1st follow-up at 90% and a response rate in the 2nd follow-up at 80%. The anticipated follow-up rate is based on experiencesfrom previous follow-up studies in Tanzania(7).
The study is grouped in five work package according to the specific objectives:

Work package 1, Acquisition patterns of high-risk (HR) human papillomavirus (HPV) with a special view to HIV status: Among women testing HR-HPV negative at baseline (Fig. 2), all women testing HIV positive (~190 from the screening clinic and 250 from HIV clinics = 440 in total) as well a random sample of 560 HPV negative/HIV negative women will be invited to a new gynecological examination after 14 months (1st follow-up visit), where a health provider cervical swab (ThinPrep) sample on all women is taken.These sampleswill all be tested for HPV using HC2 and genotyping will be performed on the HPV positive samples. At the 2nd follow-up visit (at 26 months) a health provider taken cervical swab (ThinPrep) will be obtained. All samples from the 2nd follow-up will be sent to Denmark for establishment of a cytology diagnosis and the remaining material will be sent to Germany for HC2 testing and subsequent genotyping of the HPV positives.All cytology results and HPV results will be sent back to Tanzania. In case of a positive cytology (HSIL or worse) the woman will be called in and will be treated according to the cervical cancer screening standard of care methods in Tanzania.
Based on the literature (8) we estimate an HPV acquisition rate among the initially HPV negative women at 1st follow-up of around 10%, similarly an acquisition rare of 10% from the 1st to the 2nd follow-up. The association between HR-HPV acquisition and the women's age, life style characteristics, reproductive history and HIV status will be assessed.

Work package 2, Persistence patterns of high-risk HPV types and absolute risk of severe cervical lesions focusing on the importance of HIV status: Persistence/clearance patterns of HR-HPV will be determined among all women who are HR-HPV positive at baseline(Fig. 2) (~700 from the screening clinic and 250 from the HIV clinic i.e. ~950 in total). They will be invited for follow-up examinations and tested for HR-HPV after 14 and 26 months (1st and 2nd follow-up visit). For this group of women also a self-collected cervical swab will be obtained at the 1st follow-up in 500 randomly selected women. HPV genotyping will be performed among women who are HR-HPV positive during follow-up.Women who are persistently HPV positive for the same HPV type at enrolment and at 1st follow-up will be called in for a cytological examination at the respective clinic.Also in case of a positive cytology (HSIL or worse), the women will be called in for further follow-up. HR-HPV persistence/clearance patterns will be described in relation to the women's age, life style characteristics, reproductive history, HIV status and HPV genotype. We estimate a persistence rate of 40% after 14 months and of 20% after 26 months (9). Due to the fact that a cytology diagnosis is obtained on all women at the 2nd follow-up, we will also be able to look at the absolute risk of HSIL or worse in relation to both one time HPV positivity, HPV persistence and according to HIV status.

Work package 3, Test performance of *Care*HPV testing, pap smear and VIA for detection of cervical precancerous lesions: As described above, all 4000 women enrolled will be screened by use of *Care*HPV testing, Pap smear (liquid based cytology i.e. ThinPrep) and VIA at the study baseline, and the sensitivity and specificity of *Care*HPV testing and VIA will be estimated and the positive and negative predictive values calculated. The operating

characteristics of the two screening methods will be assessed according to HIV status. All VIA positive women will subsequently be treated in agreement with thecervical cancer screening standard of care methods in Tanzania. In case of a positive cytology that was not already identified through a positive VIA, the women will be called in for further follow-up.High-quality cervical liquid-based cytology and where possible also cervical biopsies will be used as Gold Standard. Based on the samples collected at the 1st follow-up, the HPV results from the self-collected brush and the health provider collected brush will be compared.

Work package 4, Continuity of care among women who are tested are HPV positive – a comparison of two different interventions: Women who are tested HPV positive at enrolment will be randomized to either a patient navigation model or a cell phone model consisting of automated SMS messages. *Patient navigation model*: A trained community health worker will be identified as the woman's patient navigator. There will be established a one-to-one relationship between the patient navigator and the woman to address anticipated barriers such as communication difficulties and difficulties with arranging transportation. *Cell phone model***:** HPV positive women will receive automatically generated SMS messages, which will convey HPV result, send appointment reminders and health information during the first 12-14 months follow-up period.After 20 months, the continuity of care, based on the number of HPV positive women who return for the 1st follow-up examination after 14 months, will be compared. Additionally, the average time spent providing navigation from an HPV positive result is established to 12-14 months after and the associated cost will be calculated. Likewise the price of establishing and maintaining the system generating the SMS reminders will be measured. The differences in total costs and re-attendance between patient navigation and SMS reminders will be calculated. Re-attendance will be defined as HPV positive woman who re-attend within 12-14 months after the HPV positive result is established. Finally**,** HPV positive women who do not re-attend for screening after 12-14 months will be traced and interviewed. A mixed method approach, relying on structured questionnaires, in-depth interview and key informant interviews will be used to describe perceived barriers for attending 12-14 months follow-up.

Work package 5, Health service capacity building for cervical cancer prevention:Health service capacity building will be performed at primary, secondary and tertiary level. At the primary and secondary levels, key barriers for optimal use of existing communication paths for ensuring continuity of care among women diagnosed with precancerous lesions will be identified through a register based desk study. Based on the results, interview guides will be developed for in-depth interviews with health providers working at primary and secondary level and community representatives. The experiences from this assessment will be used to develop a training program in cervical cancer prevention and patient navigation that will include staff at primary and secondary health units together with community health workers in Dar es Salaam and Kilimanjaro Region. The trained community health worker will be employed as patient navigators. At tertiary level, the project will respond to the research needs set forth by ORCI and KCMC. Three PhD courses, one in Clinical Trials, one in Prevention and Control of Gynaecological Cancers and one in Policy Brief Writing will be offered at KCMC in alignment with the exiting BSU initiatives at KCMC. The PhD courses will be co-developed and co-taught by Tanzanian and Danish researchers. At both ORCI and KCMC there is a need to strengthen the capacities of researchers to undertake in-country PhD training at an international level. To address this need, four PhD studies, three Tanzanian and one Danish (co funded by SDU), will be included in the project. The Tanzanian PhD students will be recruited through public announcement of the scholarships and competitive applications.Two of the Tanzanian PhD students will be enrolled at KCMC and one at ORCI. Theywill additionally conduct 3 months of academic work each year in Denmark. The project will be performed as a twinning arrangement where the Tanzanian and the Danish PhD students will work closely together. To increase the expertise within HPV epidemiology and HPV testing in Tanzania and thereby increase the sustainability of the project outcomes, a post-doctoral fellow, Crispin Kahesa(CK), who has obtained his PhD as part of our previous research (2-6, 9) and who is presently acting as national trainer for the cervical cancer

prevention program in Tanzania, will be employed in the project. He will be visiting Institute of Medical Virology at Tuebingen University in Germany to get detailed knowledge about HPV testing and HPV analyses. In addition, to enhance local expertise in cervical cancer screening and HPV testing, a faculty exchange to the International Agency for Research on Cancer (IARC) in Lyon will also be arranged. Finally, to further upgrade CK's academic skills he will be involved as a co-supervisor of the two PhD projects focusing on Cervical Cancer Screening and Continuity of Care and write two independent papers based on the research findings.

Ethical research permissions will be obtained from the Ministry of Health in Tanzania and from local authorities in Dar es Salaam and Kilimanjaro. Ethical clearance will be obtained from the Ethical Review Board at KCMC and ORCI as well as from the Ethical Review Board of the National Institute of Medical Research. The project will follow the international ethical guidelines developed by CIOMS (Council for International Organization of Medical Sciences), placing particularemphasis on ensuring participant safety. Hence, women who have a positive cytology (HSIL or worse) will be called in and treated according to Tanzanian standard of care. Similarly, women who are persistently HPV positive will be traced, and liquid-based cytology samples will be obtained and analyzed. In case of a positive cytology result (HSILor worse), the women will be offered colposcopy directed biopsies and treatment according to the cervical cancer screening national guidelines. Informed written consent will be obtained from research participants and confidentiality guaranteed.The trial will be registered at ClinicalTrials.gov and trial analyses and reports will be made in accordance with CONSORT requirements. It is an important part of the study that all women will have a cytology examination when they exit the study after 26 months and we will make sure that all women are cared for in the best possible way.

4. Expected outputs and outcomes

The project will produce 4 PhD theses, at least 14 scientific papers published in international, peer-reviewed journals, at least 5 articles published in popular journals/magazines, at least 6 conference papers (4 national and 2 international), and a minimum of 12 research updates and policy briefs.

The expected outcomes of the project are:

- New knowledge about the natural history of HPV infection and consequences of HPV infection among HIV positive and HIV negative women
- New approaches in performing cervical cancer screening. On the basis of the research, possibleimprovements of the screening program will be identified, with a particular viewto implementation of HPV testing and improved continuity of care.
- A cadre of health staff and community health workers who are trained in cervical cancer control and prevention and who through an improved communication line will help facilitate on-going care and treatment to women who are screened positive
- Improved capacities among researchers to conduct interdisciplinary and internationally informed research on primary and secondary prevention of cervical cancer
- Decreased mortality from cervical cancer due to detection of precancerous lesions and earlier detection of cervical cancer
- Reduced poverty through enhancement of women's sexual and reproductive health. To a high degree cervical cancer is diagnosed in women at reproductive age and is thus leading to high numbers of premature deaths with substantial social and economic consequences at an individual level and in society. Prevention of cervical cancer will therefore have an impact on reduction of poverty and sustainable development in society.

5. Relevance

In Tanzania, cervical cancer is the commonest type of cancer in women, and that with the highest mortality rate. Annually, approximately 7300 new cases are diagnosed and about 4200women die from cervical cancer(11). Thus cervical cancer is a public health problem that has enormous social and economic population impact as it often affects women at reproductive

age(12). To address this public health problem, the project will provide new and important information on the natural history of HPV and how it relates to HIV, information that will be of help in the development of more efficient vaccines and screening strategies that targets HIV positive and HIV negative women. The project also aims to evaluate *Care*HPV testing (a simple to do test) as a tool for cervical cancer screening and to examine how continuity of care of women who are screened positive can be improved by two simple low cost interventions. The information generated from the project will help inform the future screening strategy in Tanzania as well as in other countries with high HIV prevalence. We will make it a priority that beside the publication of our results in scientific journals, we will communicate the results to decision makers, stakeholders and to the general population.The focus areas of our research, HPV, HIV and cervical cancer are well in line with the "Tanzanian National Health Research Policy" from 2013 that lists Communicable diseases, Non-communicable diseases and Reproductive health as top-three priority areas. Our research areas are also aligned with the Tanzanian Health Sector Strategic Plan III (HSSP III 2009-2015), supported by Danida, which also lists reproductive health and communicable and non-communicable diseases as priority areas. The project does also have relevance in relation to overall objectives and priorities of Danish development cooperation as expressed in The Right to a Better Life which states that "Denmark will be at the forefront of international efforts to promote sexual and reproductive health and rights, and in the fight against HIV/AIDS". Finally, through the linkage with KCMC, the activities are also in line with Danida priorities for research capacity building, since KCMC is one of the core institutions in the Building Stronger University (BSU) program.

6. Project plan

Since the project plan is complex and dynamic with interactions between multiple WPs, the key priorities will be to facilitate the necessary interactions between the WPs and to maintain the overall scientific direction over the life of the project. The project will start in January 2015 and end in December 2019. The existing ORCI and KCMC institutional bank accounts will be used for the project; and the existing financial and procurement regulations will be used for implementing the project in Tanzania. The main project milestones and timetable are shown on **Fig. 3**. The detailed budget is attached in the main application and it shows how the resource allocation in the project will be distributed between the institutions involved over the project period.

7. Participants, organization and management

Julius Mwaiselage is a medical doctor and epidemiologist and public health specialist. He is the Director of Cancer Prevention Services at ORCI. He has 9 years experiences in cancer epidemiological research in Tanzania and has been involved in various collaborative research projects focusing on HPV prevalence, cervical cancer screening and HPV vaccine introduction in Tanzania. He has authored more than 20 scientific papers in peer-reviewed journals and supervised 3 PhD students and more than 15 master's students. **Vibeke Rasch** is a gynaecologist and professor in global reproductive health. She has almost20 years experiences in reproductive health research in Tanzania, has acted as principal responsible party in an enhancing research capacity building project in Vietnam and has been member of the BSU steering committee. She has authored more than 100 scientific publications and supervised 16 PhD students, more than half from sub-Saharan Africa and Asia. **Susanne Krüger Kjær** is a medical doctor and professor of cancer epidemiology. Her main research areas are HPV and cancer and the importance of gene-environment interactions in cancer development with a focus on clinical utility and the translational aspect. She has authored more than 350 scientific papers, and she is the Danish primary investigator on the clinical, randomised trials of the efficacy of HPV vaccination. She has supervised more than 25 Phd students. **TwalibNgoma** is a professor of oncology. He has more than 25 years of experience in teaching, clinical work and research related to cancer. He is the executive director of ORCI and the head of clinical oncology department of Muhimbili University College of Health and Allied Science. **RachelManongi** is Head of Community Medicine Department at KCMC, she has a record of community based research with a special focus on HIV prevention and sustainable health promotion and has also been active in the establishment of a cervical cancer registry at KCMC. She has authored more than 40 papers in international journals.

The project builds on and extends existing collaboration between these Tanzanian and Danish researchers. The involved Danish researchers have solid experience in research capacity building in Tanzania and in HPV research and both have strong publication records. The proposed project will be undertaken in close coordination with the research capacity building activities conducted within the BSU initiative. The overall responsibility for the project lies with the main Tanzanian applicant. To facilitate cross-country project management, a Steering Board will be established between Tanzanian and Danish collaborators. A project management unit(PMU) will be established at ORCI. The PMU will consist of a project secretary and an accountant and will be responsible for day-to-day activities. To monitor the activities, a web-based project management tool will be established. The web tool will include detailed updated work plans linked to the work packages so partners can track project progress. Project documents will be available on the web-site. Members of the Steering Board will meet on a regular basis to ensure a continuous progress of the study. In addition, annual workshop meetings will beheld with representatives from the partner institutions.

8. Project's international dimension

There is a great international interest in cervical cancer prevention focusing on different screening modalities, HPV testing and HPV vaccination, and it is one of the areas where substantial progress has been made in recent years and it is also one of the areas where research has the greatest translational potential. The suggested project relies heavily on collaboration between researchers in Tanzania, Denmark, Germany and France who have strong expertise in HPV epidemiology, HPV testing technology, cervical cancer screening approaches, and international health. Through this international collaboration, we will obtain a strong and valuable synergy. By means of this project there will be a great opportunity for transfer of knowledge and technology to Tanzania, which in a longer perspective may be further transferred to neighbouring sub-Saharan African countries with similar high prevalence rates of HPV and HIV.

9. New knowledge

Virtually all cases of cervical cancers and high-grade precursor lesions are caused by a persistent infection with HPV(13). Although effective prophylactic vaccines against HPV have been developed, they are still relatively expensive and logistically demanding as they currently require a 3-dose regimen. Furthermore, they do not treat already existing HPV infections and related diseases. Several African cross-sectional studies of the prevalence of HPV have been performed, including our own from Tanzania where we found an HPV prevalence of 20.1% among 3700 women(2). In the same study we found that 9.3% of the women were HIV positive. In contrast, only few prospective studies on HPV epidemiology have been conducted in Africa. Of these, some had a limited sample size (14), some did only include HIV negative women(9) or exclusively used self-sampled cervical swabs(15). In spite of the fact that cervical cancer is the most common malignancy among women in Sub-Saharan Africa(1), little is known about the distribution of HPV types, independent risk factors of incidence and patterns of persistence for different HPV types. Even though HPV16 has been found to be common in sub-Saharan African women, some studies have reported HPV52 and HPV58 to be more prevalent(2). Data on which HPV types are more likely to persist in relation to HIV status are scarce, particularly in HIV positive individuals. Results from the proposed study will add important information to our knowledge about the natural history of HPV in an HIV high-risk area and will be helpful in tailoring screening programs to match the needs of HIV positive and HIV negative women.

The conventional cytology screening (Pap smear followed by colposcopically-directed biopsies) demands costly cytology laboratories with skilled and highly experienced personnel, and multiple visits at regular intervals are needed. Consequently, the Pap smear screening is neither sufficiently developed nor sustainable in less developed countries(16). Therefore, cost effective methods such as VIA have been adopted in several countries for early detection of precancerous lesions. In 2002 cervical cancer screening based on VIA was implemented at

ORCI and the program has subsequently been scaled up to cover other regions in Tanzania. However, several studies, including our own recent study, have found VIA to have a limited sensitivity(4). In contrast, HPV screening is appealing due to a higher sensitivity and a higher negative predictive value(17). However, successful HPV screening in countries with limited resources requires a simple HPV test that will perform well also in remote areas and which is affordable. Finally, self-sampling will most likely be needed to make screening practical in some settings. . In relation to these issues, our study will contribute new knowledge which can immediately be used and implemented to the benefit of the women.

A successful programme for cervical cancer prevention requires function in its entirety. The programme should ensure high levels of screening coverage of the target population, offer high quality services, have good referral systems that guarantee patient follow-up and make certain that women receive appropriate treatment. Experiences from Tanzania mainland have documented that these preconditions are often not adhered to due to a poor functioning health system and as a consequence the screening results are often not conveyed and proper action not always taken. Currently, there is no mechanism in place in Tanzania to help women navigate between the potential barriers, which may be hindering factors for obtaining confirmatory diagnosis and adequatetreatment of cervical precancerous lesions. Mobile Health, which implies the use of mobile communication devices for health care, is seen as a complementary strategy for strengthening health systems and the use of SMS has successfully been used to remind patients to take drugs and attend appointment e.g.in Kenya(18). Similarly, members of our research team have documented the effect of SMS on antenatal care attendance and skilled delivery attendance in Tanzania(7).The Patient Navigation Model is an alternative approach to enhance continuity of care among underserved populations. The navigators can be trained community health workers or peer educators who provide support and guidance (19). Patient navigation is used as a standard of care in most of Western oncological departments and has been proven to be successful in several studies e.g: Cancer control among urban African American (20) and Breast cancer screening(21). Understanding the acceptance of these two proposed models among Tanzanian women detected to have HPV will help health care professionals to develop more effective continuum of care programs by promoting attendance to HPV screening and follow-up of disease progression.

10. Publication and dissemination strategy

The research findings will be communicated via a project website, scientific paper in peer-reviewed journals and popular articles. Further to get maximum impact of the findings, a stakeholder workshop focusing on cervical cancer screening and continuity of care will be held at the beginning and at the end of the project. The invitees will include Women's groups representatives, civil society, health care providers, health sector officials and researchers. The workshop will involve stakeholders in the formulation of intervention strategies, which will enhance continuity of care among women who are screened positive. Further, at the end of the project period a policy brief workshop facilitated by a communication expert will be held and will result in the formulation of a policy brief that summarizes the research findings and provides recommendations to decision makers. The policy brief will be produced and shared at a national dissemination seminar where health policy makers, Danida representatives and other relevant stakeholder are invited.

11. Strategy for phasing out of the project

The project will be undertaken in cooperation with Ministry of Health officials and with health system representatives. Based on the research conducted within each work package, concrete recommendations for improved cervical cancer prevention will be developed and shared with health policy makers and other stakeholders. Since the PI is Director of Cancer Preventive service in Tanzania at ORCI and a member of the Ministry of Health technical working group for cervical cancer prevention and control in Tanzania, he will ensure the recommendations of the project are sent to the respective authorities and implemented. Initially most of the technical recommendations from the project will be implemented at ORCI, KCMC and among cervical cancer screening implementing partners in Tanzania after update of the cervical cancer

screening national service delivery guidelines. Furthermore, through a phased and participatory approach, the policy recommendations for the Ministry of Health, will be discussed at the relevant level of authority in order to ensure the updated policy guidelines and ministerial circulars for cervical cancer include the project recommendations on improvement, particularly on continuity of care. The Tanzanian post-doctoral and PhD students will be in the forefront in the implementation and sustainability of the comprehensive cervical cancer prevention in Tanzania given the knowledge and skills obtained in the project; and it is anticipated that they will be employed by ORCI and KCMC or even at the Ministry of Health. The established cohort of HPV positive women will be kept and maintained at ORCI for future studies on HPV persistence and clearance patterns and women's absolute risk of subsequently developing precancerous lesions (17).

Fig. 1:Natural history of human papillomavirus (HPV) infection and cervical precancerous lesions

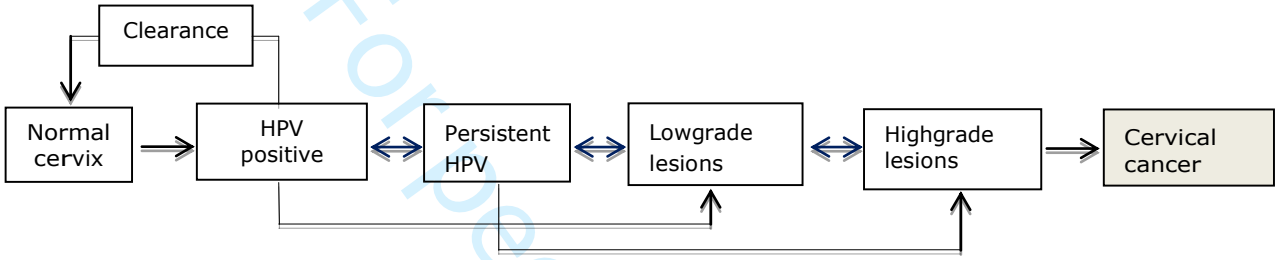
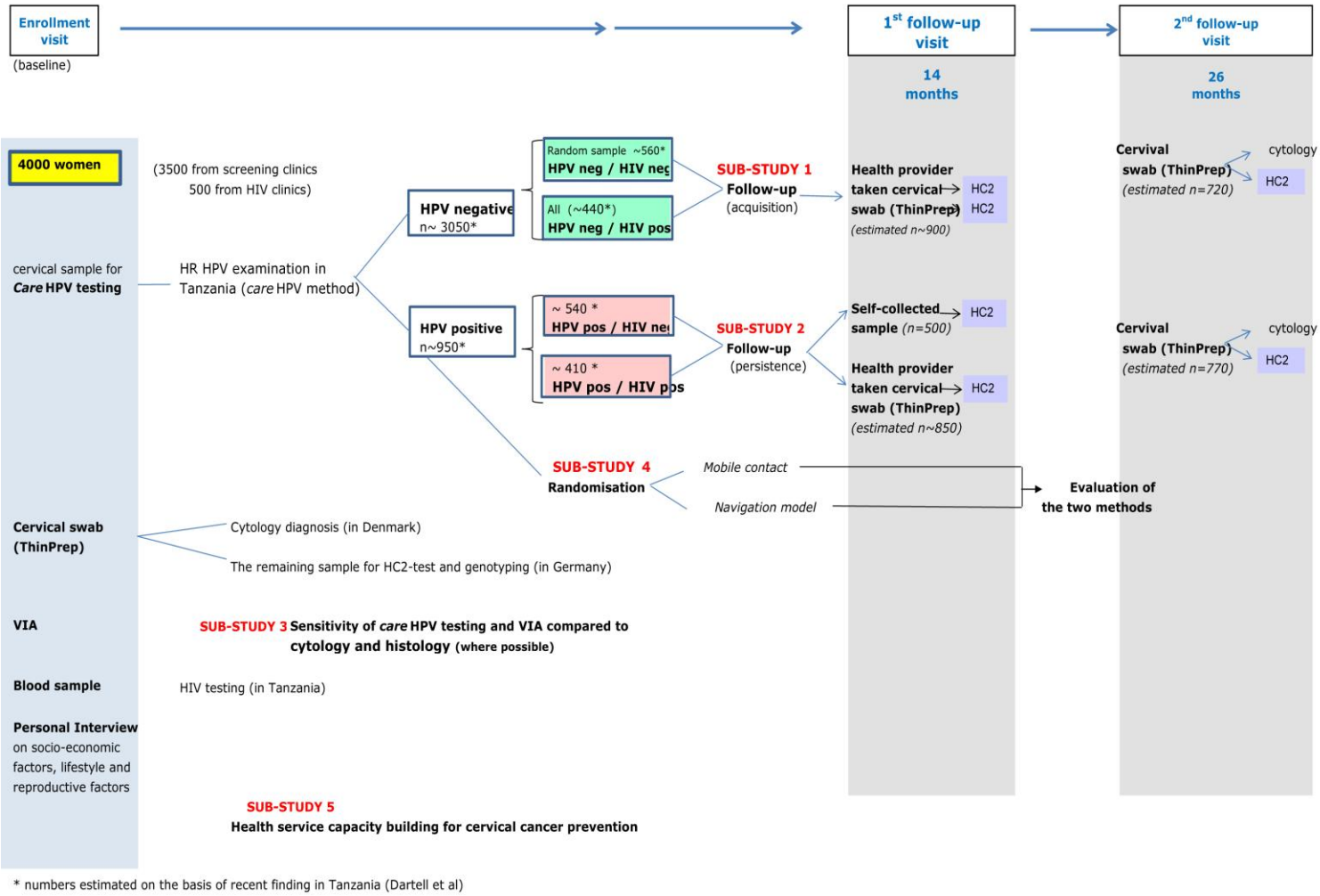


Fig 2: The schematic overview of the study design



* numbers estimated on the basis of recent finding in Tanzania (Dartell et al)

Fig 3: The schematic overview of the project milestones and timetable

FIG 3: THE SCHEMATIC OVERVIEW OF THE PROJECT MILESTONES AND TIMETABLE

MILESTONES	2015				2016				2017				2018				2019				Work packages
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	
Project commencement																					WP1,2,3,4,5
Announcement and recruitment of PhD students																					WP1,2,3,4
Enrollment of PhD students into universities																					WP1,2,3,4
PhD students attending university PhD program																					WP1,2,3,4
Establishment of research sites																					WP1,2,3,4
Recruitment and training of research assistants																					WP1,2,3,4
Data and specimen collection in Tanzania																					WP1,2,3
Randomization of women																					WP4
Assessment of continuity of care among randomized women																					WP4
Conducting PhD courses																					WP5
Postdoc fellow attached in research institution in France and Germany																					WP5
Publications																					WP1,2,3,4,5
PhD thesis submissions																					WP1,2,3,4
Defence of PhD thesis																					WP1,2,3,4
Dissemination of research findings																					WP1,2,3,4,5
Project completion and phasing out																					WP1,2,3,4,5

Note: Project commencement involves planning meeting of researchers, setting up of the project office, and ensuring ethical clearance is obtained from relevant bodies

Note: Project completion involves writing of the final project report, final auditing of the project, phasing out of the project to ensure sustainability

12. Main References

1.**Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer 2010 Dec 15;127(12):2893-917.
2.**Dartell M**, Rasch V, Kahesa C, Mwaiselage J, Ngoma T, Junge J, et al. Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study. SexuallyTransmittedDiseases. 2012 Mar;39(3):201-8.
3. **Dartell M**, Rasch V, Munk C, Kahesa C, Mwaiselage J, Iftner T, et al. Risk factors for high-risk human papillomavirus detection among HIV-negative and HIV-positive women from Tanzania. SexuallyTransmittedDiseases. 2013 Sep;40(9):737-43.
4. **Dartell MA**, Rasch V, Iftner T, Kahesa C, Mwaiselage JD, Junge J, et al. Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative Tanzanian women. International Journal of Cancer 2014 Jan 4. PubMed PMID: 24391021. Epub 2014/01/07. Eng.
5. **Kahesa C**, Kjaer S, Mwaiselage J, Ngoma T, Tersbol B, Dartell M, et al. Determinants of acceptance of cervical cancer screening in Dar es Salaam, Tanzania. BMC Public Health. 2012;12:1093.
6. **Kahesa C**, Kjaer SK, Ngoma T, Mwaiselage J, Dartell M, Iftner T, et al. Risk factors for VIA positivity and determinants of screening attendances in Dar es Salaam, Tanzania. BMC Public Health. 2012;12:1055. PubMed PMID: 23216752.
7. **Lund S**, Hemed M, Nielsen BB, Said A, Said K, Makungu MH, et al. Mobile phones as a health communication tool to improve skilled attendance at delivery in Zanzibar: a cluster-randomised controlled trial. BJOG 2012 Sep;119(10):1256-64. PubMed PMID: 22805598.
8. **Nielsen A**, Iftner T, Munk C, Kjaer SK. Acquisition of high-risk human papillomavirus infection in a population-based cohort of Danish women.Sexually Transmitted Diseases 2009 Oct;36(10):609-15.
9. **Fukuchi E**, Sawaya GF, Chirenje M, Magure T, Tuveson J, Ma Y, et al. Cervical human papillomavirus incidence and persistence in a cohort of HIV-negative women in Zimbabwe. Sexually Transmitted Diseases. 2009 May;36(5):305-11. PubMed PMID: 19295468.
10. **Olesen TB**, Iftner T, Mwaiselage J, Kahesa C, Rasch V, Ngoma T, et al. Prevalence and type distribution of human papillomavirus among 1813 men in Tanzania and the relationship to HIV status. Sexually Transmitted Diseases. 2013 Jul;40(7):592-8. PubMed PMID: 23965778. Epub 2013/08/24. eng.
11. Human Papillomavirus and Related Diseases in Tanzania. Summary Report [Internet]. ICO Information Centre on HPV and Cancer.
12. **Chokunonga E**, Borok MZ, Chirenje ZM, Nyakabau AM, Parkin DM. Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991-2010. International Journal of Cancer 2013 Aug 1;133(3):721-9. PubMed PMID: 23364833. Epub 2013/02/01. eng.
13. **Kjaer SK**, van den Brule AJ, Bock JE, Poll PA, Engholm G, Sherman ME, et al. Human papillomavirus--the most significant risk determinant of cervical intraepithelial neoplasia. International Journal of Cancer 1996 Mar 1;65(5):601-6.
14.**Veldhuijzen NJ**, Vyankandondera J, van de Wijgert JH. HIV acquisition is associated with prior high-risk human papillomavirus infection among high-risk women in Rwanda. AIDS (London, England). 2010 Sep 10;24(14):2289-92. PubMed PMID: 20613457. Epub 2010/07/09. eng.
15. **Safaeian M**, Kiddugavu M, Gravitt PE, Gange SJ, Ssekasanvu J, Murokora D, et al. Determinants of incidence and clearance of high-risk human papillomavirus infections in rural Rakai, Uganda. Cancer Epidemiology, Biomarkers &Prevention 2008 Jun;17(6):1300-7.
16. **Denny L**. Cytological screening for cervical cancer prevention. Best practice & research Clinical obstetrics & gynaecology. 2012 Apr;26(2):189-96. PubMed PMID: 22071306. Epub 2011/11/11. eng.
17. **Kjaer SK**, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. Journal of the National Cancer Institute. 2010 Oct 6;102(19):1478-88. PubMed PMID: 20841605.
18. **Lester RT**, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. 2010 Nov 27;376(9755):1838-45. PubMed PMID: 21071074.
19. **Honeycutt S**, Green R, Ballard D, Hermstad A, Brueder A, Haardorfer R, et al. Evaluation of a patient navigation program to promote colorectal cancer screening in rural Georgia, USA. Cancer. 2013 Aug 15;119(16):3059-66. PubMed PMID: 23719894.
20. **Halbert CH**, Briggs V, Bowman M, Bryant B, Bryant DC, Delmoor E, et al. Acceptance of a community-based navigator program for cancer control among urban African Americans. Health education research. 2014 Feb;29(1):97-108. PubMed PMID: 24173501.
21. **Lee JH**, Fulp W, Wells KJ, Meade CD, Calcano E, Roetzheim R. Patient navigation and time to diagnostic resolution: results for a cluster randomized trial evaluating the efficacy of patient navigation among patients with breast cancer screening abnormalities, Tampa, FL. PloS one. 2013;8(9):e74542. PubMed PMID:

Study number

ConcepT

Comprehensive Prevention of Cervical Cancer in Tanzania

Study site: ORCI ☐ **KCMC** ☐ **MAGOMENI** ☐ **MAWENZI** ☐

Date _____ **Study number** _____

Health Provider Initials _____ **Participant initials** _____

BACKGROUND

1. **How old are you?** ☐☐ years

2. **Are you:**

Married, monogamous	1 ☐
Married, polygamous	2 ☐
Cohabiting	3 ☐
Single, with regular partner	4 ☐
Single, no regular partner	5 ☐
Divorced/ Widow	6 ☐

How long have you known your husband / cohabiter / regular partner?

☐☐ years ☐☐ months

3. **With whom are you presently living?**

Husband / cohabiter	1 ☐
Parents	2 ☐
Parents in law	3 ☐
Other relatives	4 ☐
Friends	5 ☐
Nobody	6 ☐

4. What is the highest level of formal education you have completed?

No formal education	1 ☐
Standard 1-4	2 ☐
Standard 5-7	3 ☐
Form 1-4	4 ☐
Form 5-6	5 ☐
University/college	6 ☐
Other _____ **Specify**	8 ☐

5. What is your religion?

Christian	1 ☐
Muslim	2 ☐
Other _____ **Specify**	3 ☐

LIFESTYLE HABITS AND HEALTH

6. Do you smoke cigarettes?

.

Yes, every day	☐ 1
Yes, at least once a week	☐ 2
Yes, but less than once a week	☐ 3
No, but I previously smoked	☐ 4
No, never → (go to question 11)	☐ 5

7. How old were you, when you started to smoke cigarettes regularly?

(i.e. at least once a week)

age _____ years

8. How many years have you smoked cigarettes regularly? (subtract periods of smoking cessation)

number of years: _____

9. **If you are a current smoker, how much do you smoke on an average day?**

number of cigarettes: _____

10. **If you no longer smoke cigarettes, how old were you when you stopped smoking?**

age _____ years

11. **Have you ever drunk alcohol and if yes, how old were you when you started drinking alcohol?**

Have never been drinking	12 years or younger	13-14 years	15-16 years	17-18 years	19-20 years	21 years or older
☐ 1 (Go to question 14)	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

12. **How much per week do you usually drink of the following types of alcohol?**

Beer	No. of glasses per week on average	
Local brew	No. of drinks per week on average	
Wine	No. of glasses per week on average	
Liquor	No. of drinks per week on average	

(**1 bottle of vine** = 6 glasses, **1 bottle of liquor** = 20 drinks, **1 bottle of beer** = 2 glasses)

13. **How many times per month on average do you have more than 6 drinks on the same occasion?**

Never	Less than once a month	1-3 times per month	4-8 times per month	≥ 9 times per month
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

14. **How do you regard your own health?**

Excellent	Very good	Good	Less good	Bad
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

15. How do you perceive your body size?

Much too thick	A little too thick	Good	A little too thin	Much too thin
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

REPRODUCTIVE HEALTH and SEXUAL HABITS

16. Have you ever been pregnant?

- yes	1 ☐	
- no	2 ☐	→ **Go to question 17**

If yes:

Total number of pregnancies	1 ☐☐
Total number of births	2 ☐☐

How old were you at the first pregnancy? ☐☐ years

How old were you when you gave birth to your first child? ☐☐ years

17. Did you ever have a sexual partner?

- yes	1 ☐	
- no	2 ☐	**Go to question 21**

If yes:

How old were you at first intercourse? ☐☐ years

How old was your first partner at that time? ☐☐ years

18. How many sexual partners did you have during your lifetime? ☐☐ number

19. Did you have sexual intercourse within the last 12 months?

- yes	1 ☐
- no	2 ☐

If yes:

How often have you used condoms during the last 12 months?

At every sexual intercourse	1 ☐
Frequently but not at every intercourse	2 ☐
Rarely	3 ☐
Only sexual intercourse without condoms	4 ☐

20. Is your husband / cohabiter / regular partner circumcised?

Yes	1 ☐
No	2 ☐
No husband / cohabiter / regular partner	3 ☐

21. Has a doctor or other health care provider told you that you had genital warts (condyloma)?

- yes	1 ☐
- no	2 ☐

If yes:

How old were you when you had genital warts for the first time? ☐☐ years

Have you had genital warts in the last 12 months?

- yes	1 ☐
- no	2 ☐

22. Have you ever been screened against cervical cancer?

- yes	1 ☐
- no	2 ☐

If yes:

Has a doctor or other health care provider told you that you had precancerous lesions on the cervix?

- yes	1 ☐	
- no	2 ☐	**Go to question 23**

When did you have your last diagnose of precancerous lesions?

☐☐ calendar month ☐☐☐☐ calendar year

Which treatment did you receive?

- Cryo therapy	1 ☐
- LEEP	2 ☐
- Don't know	3 ☐

23. Has a doctor or other health care provider told you that you had one of the following sexually transmitted diseases?

Chlamydia	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years
Gonorrhea	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years
Syphilis	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years

24. Have you ever been tested for HIV?

- yes	1 ☐
- no	2 ☐

If yes:

Have you ever tested positive?

- yes	1 ☐	
- no	2 ☐	**Go to question 25**

If yes:

When did you test positive? ☐☐ calendar month ☐☐☐☐ calendar year

When did you have your last CD4 count test?
(If more than 6 months ago → refer the woman for a new test)

☐☐ calendar month ☐☐☐☐ calendar year

What was the result of the CD4 count? _____number

Have you ever been started on ARV treatment?

- yes	1 ☐
- no	2 ☐

If yes:

				started when ?	
First line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year
Second line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year
Third line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year

What is your CTC card number? _____ Clinic name _____ Card number

What is your CTC file number? _____ File number

If you do not know, can we call you and get the number?

- yes	1 ☐
- no	2 ☐

TAARIFA KUHUSU SARATANI YA SHINGO YA KIZAZI
(KNOWLEDGE OF CERVICAL CANCER)

25. Sentensi zifuatazo zinahusu saratani ya shingo ya kizazi. Sema kweli au si kweli kwa kila sentensi

(Here are some statements about cervical cancer. I will ask you to answer which are true and which are false)

1. Malaria (mbu) inasababisha saratani ya shingo ya kizazi *(Malaria (mosquito) causes cervical cancer)*	Kweli ☐	Si kweli ☐
2. Kupata maumivu wakati wa kukojoa ni dalili ya saratani ya shingo ya kizazi *(Pain during urination can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
3. Saratani ya shingo ya kizazi ndiyo inayoongoza kwa magonjwa ya kanza za wanawake hapa Tanzania *(Cervical cancer is the most commen cancer disease among Tanzanian women)*	Kweli ☐	Si kweli ☐
4. Unaweza kupata saratani ya shingo ya kizazi kwa kubusiana *(You can get cervical cancer from deep kissing)*	Kweli ☐	Si kweli ☐
5. Inawezekana kujikinga na saratani ya shingo ya kizazi *(It is possible to prevent cervical cancer)*	Kweli ☐	Si kweli ☐
6. Kutokwa damu ukeni ni dalili kuu ya ugonjwa wa saratani ya shingo ya kizazi *(Vaginal bleeding is the most common sign of cervical cancer)*	Kweli ☐	Si kweli ☐
7. Jua kali linaweza kusababisha saratani ya shingo ya kizazi *(Too much sun can lead to cervical cancer)*	Kweli ☐	Si kweli ☐
8. Maambukizi ya kwenye shingo ya kizazi mara zote hubadilika kuwa saratani *(A cervical infection will always turn into cancer)*	Kweli ☐	Si kweli ☐
9. Wanawake wenye VVU wako kwenye hatari kubwa ya kupata saratani ya shingo ya kizazi *(HIV-positive women have higher risk of developing cervical cancer)*	Kweli ☐	Si kweli ☐
10. Saratani ya shingo ya kizazi mara nyingi hugundulika mapema kutokana na dalili zake (Cervical cancer is often found at an early stage due to obvious symptoms)	Kweli ☐	Si kweli ☐
11. Unaweza kupata saratani ya shingo ya kizazi kwa kujamiiana bila kinga *(You can get cervical cancer from unprotected sexual intercourse)*	Kweli ☐	Si kweli ☐
12. Kupima afya kunaweza kugundua maambukizi ya kwenye shingo ya kizazi na kuyazuia yasibalike kuwa saratani *(Screening can detect cervical infections so they do not develop into cancer)*	Kweli ☐	Si kweli ☐
13. Saratani ya shingo ya kizazi inaongoza kwa kusababisha vifo vinavyotokana na saratani kwa wanawake hapa Tanzania *(Cervical cancer is the main cause of cancer-related death among Tanzanian women)*	Kweli ☐	Si kweli ☐
14. Saratani ya shingo ya kizazi mara nyingi huwapata wanawake wakiwa kwenye miaka ya ishirini. *(Cervical cancer is most common for women in their 20's)*	Kweli ☐	Si kweli ☐
15. Kuwashwa ukeni kunaweza kuwa ni dalili ya saratani ya shingo ya kizazi *(Itchiness in the vaginal area can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
16. Kirusi kinachoitwa Human papilloma virus ndicho kisababishacho saratani ya shingo ya kizazi *(A virus called "Humanpapiloma virus" (HPV) causes cervical cancer)*	Kweli ☐	Si kweli ☐

UKUBALI WA UJUMBE MFUPI KUPITIA SIMU YA MKONONI
(ACCEPTANCE OF MOBILE MESSAGES)

UTANGULIZI *(Introduction):*
Kwenye utafiti huu wanawake watatakiwa kurudi baada ya miezi 14. Baadhi ya wanawake watatumiwa ujumbe kupitia simu ya mkononi wenye taarifa za afya na kukukumbusha siku ya kurudi kliniki. Nitakuuliza maswali machache kuhusu ujumbe wa kupitia simu ya mkononi

(In this study, all women will get a new appointment at the clinic after 14 months. However, some women will also receive health information and reminders of their appointment via sms. Here are some questions about mobile messages.)

26. Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au ya familia yako? (Chagua tabasamu sahihi kuonyesha utakavyojisikia)

(How do you feel about receiving health information and reminders of your appointment via sms on your or your family's mobile phone? Choose the one smiley that best shows how you feel)

Siipendi kabisa
I do not like it at all ☐

Siipendi
I do not like it ☐

Sio sawa
It is not okay ☐

Sawa
It is okay ☐

Naipenda
I like it ☐

Naipenda sana
I like it very much ☐

27. Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au ya familia yako? (Weka alama ya mstari wima kuonyesha utakavyojisikia).

(How do you feel about receiving health information and reminders of your appointment via sms on your or your family's mobile phone? Make one vertical mark on the line similar to how you feel)

Thanks a lot for your help

If there are any comments to add, please write them below

_____
Baseline Study number

_____
Follow-up Study number

ConcepT

Comprehensive Prevention of Cervical Cancer in Tanzania

FOLLOW-UP QUESTIONNAIRE

Study site: ORCI ☐ **KCMC** ☐ **MAWENZI** ☐

Date _____ **Follow-up Study number** _____

Baseline Study number_____

Health Provider Initials _____ **Participant initials** _____

REPRODUCTIVE HEALTH and SEXUAL HABITS

1. Have you given birth since your last screening visit?

- yes	1 ☐	
- no	2 ☐	→ **Go to question 2**

If yes:

Total number of pregnancies since last visit	1 ☐☐
Total number of births since last visit	2 ☐☐

2. Did you have a sexual partner since your last screening visit?

- yes	1 ☐	
- no	2 ☐	**Go to question 3**

If yes:

Have you had a *new* sexual partner since your last screening visit?

- yes	1 ☐
- no	2 ☐

How many sexual partners did you have since your last screening visit?

|__|__|__| number

How often have you used condoms since your last screening visit?

At every sexual intercourse	1 ☐
Frequently but not at every intercourse	2 ☐
Rarely	3 ☐
Only sexual intercourse without condoms	4 ☐

3. Is your husband / cohabiter / regular partner circumcised?

Yes	1 ☐
No	2 ☐
No husband / cohabiter / regular partner	3 ☐

Hormonal Family Planning

4. Have you ever used hormonal family planning methods?

- yes	1 ☐	
- no	2 ☐	**Go to question 5**

If yes:

What type of hormonal contraceptives have you used?

Type	No, never	Yes	If *yes*, how long have you used it overall?
Birth control pills	2 ☐	1 ☐	☐☐ years and ☐☐ months
Birth control shot (Depo-provera)	2 ☐	1 ☐	☐☐ years and ☐☐ months
Birth control implant (Implanon/ Nexoplan)	2 ☐	1 ☐	☐☐ years and ☐☐ months
Hormonal IUD (Mirena)	2 ☐	1 ☐	☐☐ years and ☐☐ months

HIV

5. Have you tested positive for HIV since your last screening visit?

- yes	1 ☐	
- no	2 ☐	**Go to question 6**

If yes:

When did you test positive? ☐☐ calendar month ☐☐☐☐ calendar year

When did you have your last CD4 count test?
(If more than 6 months ago → refer the woman for a new test)

☐☐ calendar month ☐☐☐☐ calendar year

What was the result of the CD4 count? _____number

Have you ever been started on ARV treatment?

- yes	1 ☐
- no	2 ☐

If yes:

		started when ?	
First line	1 ☐ Yes 2 ☐ No	**If yes**	☐☐ calendar month ☐☐☐☐ calendar year
Second line	1 ☐ Yes 2 ☐ No	**If yes**	☐☐ calendar month ☐☐☐☐ calendar year
Third line	1 ☐ Yes 2 ☐ No	**If yes**	☐☐ calendar month ☐☐☐☐ calendar year

What is your CTC card number? _____ Clinic name _____ Card number

What is your CTC file number? _____ File number

If you do not know, can we call you and get the number?

- yes	1 ☐
- no	2 ☐

ATTENDANCE TO FOLLOW-UP APPOINTMENT

6. Which of following tools were most important for you to remember your appointment today? *(choose one answer)*

I remembered from my appointment card and came to the clinic	1 ☐	**Go to question 8**
I had a sms-reminder and came to the clinic	2 ☐	**Go to question 8**
A nurse called me and told me to come to the clinic	3 ☐	**Go to question 7**
A nurse visited me at home and told me to come to the clinic	4 ☐	**Go to question 7**
A nurse visited and we had the appointment at my home	5 ☐	**Go to question 7**

7. What are the main reasons why you did not come to the clinic before the nurse contacted you?

I could not afford transportation on my own	Yes 1 ☐	No 2 ☐
I did not think the appointment was important	Yes 1 ☐	No 2 ☐
I had forgotten	Yes 1 ☐	No 2 ☐
I was nervous about the result of the screening	Yes 1 ☐	No 2 ☐
I was nervous about having a gynaecological examination	Yes 1 ☐	No 2 ☐
House chores prevented me from coming	Yes 1 ☐	No 2 ☐
The clinic is too far away from my home	Yes 1 ☐	No 2 ☐
Rainy season/ public holidays	Yes 1 ☐	No 2 ☐
My family does not know that I go, so I have to go secretely	Yes 1 ☐	No 2 ☐
I had my period	Yes 1 ☐	No 2 ☐
I was pregnant	Yes 1 ☐	No 2 ☐
I had moved	Yes 1 ☐	No 2 ☐
Other *(please write)* ……		

HEALTH EDUCATION BY MOBILE PHONE
(ELIMU YA AFIA QUA SIM)

8. Have you received any text messages (sms) regarding cervical cancer and your screening appointment at the clinic?

- yes 1 ☐	
- no 2 ☐	**(Questionnaire is <u>finished</u>)**

<u>If yes:</u>

How do you like the number of messages that you received?

Too many messages	1 ☐
Adequate amount of messages	2 ☐
Too few messages	3 ☐

How do you feel about of the following statements? *(If 'don't know' leave box empty)*

The information in the messages was easy to understand	Yes 1☐	No 2☐
I did *not* need help from others to read the messages	Yes 1☐	No 2☐
The information in messages made me uncomfortable	Yes 1☐	No 2☐
I know how to read text messages on my phone	Yes 1☐	No 2☐
I often send and receive text messages on my phone	Yes 1☐	No 2☐
I shared the health education that I got on my phone with friends or family	Yes 1☐	No 2☐
I would like to continue to receive health information by mobile phone	Yes 1☐	No 2☐
My husband or other family members was happy that I received health information on my mobile phone	Yes 1☐	No 2☐
I would recommend a friend or a family member to receive health education by mobile phone	Yes 1☐	No 2☐

How do you feel about receiving health information and reminders of your appointment via sms on your mobile? *(Choose the one smiley that best shows how you feel)*

Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au? (Chagua tabasamu sahihi kuonyesha utakavyojisikia)

I do not like it at all ☐

I do not like it ☐

It is not okay ☐

It is okay ☐

I like it ☐

I like it very much ☐

Here are some statements about cervical cancer. I will ask you to answer which are true and which are false? *(only for women that have received sms'!)*

Sentensi zifuatazo zinahusu saratani ya shingo ya kizazi. Sema kweli au si kweli kwa kila sentensi

1. Malaria (mbu) inasababisha saratani ya shingo ya kizazi *(Malaria (mosquito) causes cervical cancer)*	Kweli ☐	Si kweli ☐
2. Kupata maumivu wakati wa kukojoa ni dalili ya saratani ya shingo ya kizazi *(Pain during urination can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
3. Saratani ya shingo ya kizazi ndiyo inayoongoza kwa magonjwa ya kanza za wanawake hapa Tanzania *(Cervical cancer is the most commen cancer disease among Tanzanian women)*	Kweli ☐	Si kweli ☐
4. Unaweza kupata saratani ya shingo ya kizazi kwa kubusiana *(You can get cervical cancer from deep kissing)*	Kweli ☐	Si kweli ☐
5. Inawezekana kujikinga na saratani ya shingo ya kizazi *(It is possible to prevent cervical cancer)*	Kweli ☐	Si kweli ☐
6. Kutokwa damu ukeni ni dalili kuu ya ugonjwa wa saratani ya shingo ya kizazi *(Vaginal bleeding is the most common sign of cervical cancer)*	Kweli ☐	Si kweli ☐
7. Jua kali linaweza kusababisha saratani ya shingo ya kizazi *(Too much sun can lead to cervical cancer)*	Kweli ☐	Si kweli ☐
8. Maambukizi ya kwenye shingo ya kizazi mara zote hubadilika kuwa saratani *(A cervical infection will always turn into cancer)*	Kweli ☐	Si kweli ☐
9. Wanawake wenye VVU wako kwenye hatari kubwa ya kupata saratani ya shingo ya kizazi *(HIV-positive women have higher risk of developing cervical cancer)*	Kweli ☐	Si kweli ☐
10. Saratani ya shingo ya kizazi mara nyingi hugundulika mapema kutokana na dalili zake (Cervical cancer is often found at an early stage due to obvious symptoms)	Kweli ☐	Si kweli ☐
11. Unaweza kupata saratani ya shingo ya kizazi kwa kujamiiana bila kinga *(You can get cervical cancer from unprotected sexual intercourse)*	Kweli ☐	Si kweli ☐
12. Kupima afya kunaweza kugundua maambukizi ya kwenye shingo ya kizazi na kuyazuia yasibalike kuwa saratani *(Screening can detect cervical infections so they do not develop into cancer)*	Kweli ☐	Si kweli ☐
13. Saratani ya shingo ya kizazi inaongoza kwa kusababisha vifo vinavyotokana na saratani kwa wanawake hapa Tanzania *(Cervical cancer is the main cause of cancer-related death among Tanzanian women)*	Kweli ☐	Si kweli ☐
14. Saratani ya shingo ya kizazi mara nyingi huwapata wanawake wakiwa kwenye miaka ya ishirini. *(Cervical cancer is most common for women in their 20's)*	Kweli ☐	Si kweli ☐
15. Kuwashwa ukeni kunaweza kuwa ni dalili ya saratani ya shingo ya kizazi *(Itchiness in the vaginal area can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
16. Kirusi kinachoitwa Human papilloma virus ndicho kisababishacho saratani ya shingo ya kizazi *(A virus called "Humanpapiloma virus" (HPV) causes cervical cancer)*	Kweli ☐	Si kweli ☐

Thanks a lot for your help

If there are any comments to add, please write them below

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Indicated as Cohort in all appropriate sections
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Indicated in the section "abstract"
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Explanation provided in the "Introduction "section
Objectives	3	State specific objectives, including any prespecified hypotheses	These has been provided in ll. "108-113"
Methods			
Study design	4	Present key elements of study design early in the paper	Indicated in the sub section "study design and study population", ll. 117-143.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Indicated in the sub sections "study design and study population", ll. 117-143; "assessment of exposure, ll. 147-195; "outcome measures; ll. 198-205; "table 1: Overview of data collected in the CONCEPT cohort"
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Indicated in the sub sections "study design and study population", ll. 117-143; "assessment of exposure, ll. 147-195; "outcome measures; ll. 198-205.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA - No matching was done
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Indicated in the sub sections "assessment of exposure, ll. 147-195; "outcome measures; ll. 198-205
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Description of this item has been provided in table 1- Overview of data collection
Bias	9	Describe any efforts to address potential sources of bias	This has been described in section

			"What is being measured"
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	An overview of data management has been provided in the sub section "Data management, ll 208-214. Detailed description of the statistical analysis may be provided in the respective individual articles,
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	An overview of data management has been provided in the sub section "Data management, ll 208-214. Detailed description of the statistical analysis may be provided in the respective individual articles
		(*b*) Describe any methods used to examine subgroups and interactions	An overview of data management has been provided in the sub section "Data management, ll 208-214. Detailed description of the statistical analysis may be provided in the respective individual articles
		(*c*) Explain how missing data were addressed	Missing data selected variables are described in Table 1 and Table 2.
		(*d*) If applicable, explain how loss to follow-up was addressed	Indicated in the sub sections "study design and study population", ll. 117-143.
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	This information has been provided in the flow chart, figure 1.
		(b) Give reasons for non-participation at each stage	This information has been provided in the flow chart, figure 1
		(c) Consider use of a flow diagram	Flow chart has been provided, figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures	Relevant characteristics of the

		and potential confounders	participants and their distribution has been provided in Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Information on missing values has been provided for each variable in Table 2 & Table 3
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2 and 3 provide a measure of important events at a baseline and follow-up
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 provides Confidence interval of the important outcome measures at baseline and on follow up
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA. Cohort profile. However, summarized in "abstract".
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Indicated in the section "Strengths and limiations, ll. 264-273
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA. Cohort profile
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA. Cohort profile. However, a the section "future plans", ll. 276-284 indicates future perspectives for the cohort.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Inidicated in the section "financial disclosure, ll. 294-296.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Cohort profile: The comprehensive cervical cancer prevention in Tanzania (CONCEPT) study

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Cohort profile: The comprehensive cervical cancer prevention in Tanzania (CONCEPT) study

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Abstract

Purpose

Cervical cancer is a major cause of death among women in Eastern Africa, and the distribution of HPV in relation to HIV-status is inadequately characterised in this region. In order to guide future cervical cancer preventive strategies that involve HPV-testing, the Comprehensive Cervical Cancer Project in Tanzania (CONCEPT) study was established in 2015. The CONCEPT cohort aims to investigate the natural history of HPV and determine acquisition and persistence patterns of high-risk (HR) HPV– both group- and type-specific – among HIV-positive and -negative women. Further, the influence of lifestyle and sexual/reproductive factors will be investigated.

Participants

Women aged 25-60 years were enrolled from cervical cancer screening clinics in Dar-es-Salaam and Moshi, Tanzania. Data were collected at baseline, at 14 months (1st follow-up), and at 28 months (2nd follow-up). Biological samples included two cervical swabs for *care*HPV DNA-testing, cytology, Hybrid Capture 2, genotyping, and blood samples for HIV. Visual inspection with acetic acid was performed, and socio-demographic, lifestyle, and sexual/reproductive characteristics were collected through a standardised questionnaire.

Findings to date

4043 women were included in the cohort from August 2015 – May 2017. At baseline, 696 (17.1%) women were HR HPV-positive and among these 31.6% were HIV-positive; 139 women (3.4%) had high grade squamous intraepithelial lesions. 3074 women (81%) attended the 1st follow-up. The majority attended after receiving a phone call reminder (35%) or from home via self-samples (41%). At 1st follow-up, 438 (14.4%) were HR HPV-positive and 30.4% of these were HIV-positive.

Future plans

A second follow-up is underway (17 December 2018 – October 2020). We plan to integrate our data with a previous cross-sectional HPV study from Tanzania to increase the power of our findings. Researchers interested in collaborating are welcomed, either by extracting data from or jointly requesting further investigation from the cohort.

Registration

ClinicalTrials.gov: NCT02509702 (CONCEPT sub-study).

Strengths and limitations of this study

- This is a large-scale longitudinal cervical cancer study conducted in an HIV endemic population that aims to address a major cause of disease among East-African women, which so far has not received much focus within global health research.
- Women are followed over a long duration of time and with a large amount of data being collected by use of questionnaires and lab tests.
- It was difficult to get women to return for follow-up screenings. However, carefully designed tracing plans and dedicated home-visiting staff entailed that we managed to attain an 81% participation rate at 1st follow-up.
- Detailed HIV documentation was challenging to obtain, which has limited our ability and power in analyses involving HIV immunologic markers and treatment.

Introduction

Cervical cancer is a major cause of cancer-related mortality and morbidity globally. The highest prevalence is found among women aged 45-60 years[1], and the burden of disease is disproportionally distributed among low- and middle-income countries (LMIC) and high-income countries (HIC)– LMICs account for 80% of cervical cancer cases worldwide. The global age-standardised incidence rate for cervical cancer is 14 per 100,000 women[2] while the incidence rate of cervical cancer is 42.7 per 100,0000 women in East Africa[3] and 54 per 100,000 women in Tanzania, specifically[4]. Major contributing factors to the high burden of disease in resource-limited settings includes low awareness of the disease and how to prevent it; unavailability of organised screening programmes; and use of visual inspection with acetic acid (VIA) as standard screening method which has shown to have low sensitivity when it is performed by unskilled health provider with inadequate supportive supervision[5 6 7].

HPV is the most common sexually transmitted infection worldwide, and there is a 60-70% life-time risk of acquiring an HPV infection among sexually active women[8]. Eighty to 90% of HPV infections clear spontaneously, however 10-20% become persistent and can develop into pre-cancerous lesions and cervical cancer over time. There are different factors associated with HPV persistence, the two most significant ones are the type of HPV involved and immunodeficiency, hence HIV-positive women have increased risk of acquiring HPV[9] and for the infection to become persistent[10 11]. HPV16 and 18 are the two most important types as these are associated with approximately 70% of all invasive cervical cancers worldwide[8]. Globally, the five most common types are HPV16, 18, 52 ,31, and 58[5 6]. However, cross-sectional studies from Africa and systematic reviews on the global HPV burden indicate that the type-specific prevalence of HPV differs in Africa compared to other regions[2 12 13], specifically HPV 52, 58, 31, and 35 are more common in African countries compared to other parts of the world[14-16]. Further, sexual, reproductive, and lifestyle factors influence HPV acquisition and persistence, including smoking, high parity, number of sexual partners, long-term use of oral contraceptives, and co-infections with other sexually transmitted agents[17 18]. However to date, there are no adequately powered longitudinal HPV studies among middle-aged women in East Africa

that explore the association of HIV, immunological factors, reproductive, and lifestyle factors on HR HPV acquisition and persistence.

To our knowledge, only two HPV cohort studies and one large HPV cross-sectional study have been conducted in Africa, which explore the dynamics of HPV,HIV, and cervical cancer, namely (I) the HPV in Africa Research Partnership (HARP) HPV Study in Burkina Faso and Tanzania[19]; (II) the African Collaborative Center for Microbiome and Genomics Research (ACCME) study in Nigeria[20]; and (III) the Prevention of Cervical Cancer in Tanzania (PROTECT) study[21]. Other studies are nested in HPV vaccine trials[22-24]. These studies have provided some insight into the distribution of HPV among different African populations, however, they were either cross-sectional or conducted among adolescents' with inadequately powered HIV-positive women and with a relatively short duration of follow-up.

The Comprehensive Cervical Cancer Prevention in Tanzania (CONCEPT) study was launched in 2015 with an overall aim of improving prevention of cervical cancer in Tanzania (online supplementary appendix 1). The CONCEPT study is an international collaborative study between Ocean Road Cancer Institute (ORCI), Kilimanjaro Christian Medical Centre (KCMC), University of Southern Denmark, and the Danish Cancer Society Research Center. The CONCEPT study has several specific objectives; (I) To investigate the natural history of HPV and its associated factors; (II) To determine the feasibility and acceptability of HPV self-sampling[29] and the test performance of *care*HPV compared to (HC2) and VIA[6]; and (III) how to ensure follow-up of HPV-positive women, and elucidate what motivates or prevents these women from attending to follow-up visits[25 26 27]. Introduction of HPV DNA testing in LMIC is challenging due to logistical problems inherent in these settings, however, HPV-based primary screening is a key method in future screening programmes across the world[28], and for it to be effectively established in resource-limited settings, local specific evidence is warranted. The aim of this article is to describe how this cohort was established and followed up, the profile of the cohort, and provide some characteristics of the cohort at enrolment and at the 1st follow-up. The specific objectives of the CONCEPT study have been and will be published in separate papers[6 26 29-32].

Cohort description

Study design and study population

This study was conducted in Tanzania, which is a low income country located in Eastern African with a population of 56 million people[33]. Women were enrolled from three existing cervical cancer screening clinics located in urban and semi-rural areas; (1) ORCI in Dar-es-Salaam as well as (2) KCMC and (3) Mawenzi regional referral hospital in the Kilimanjaro region. ORCI is a national cancer hospital that provides clinical care and treatment for all the cancer patients in the country. Additionally, they conduct cervical cancer screening clinics three times a week for general population. KCMC Hospital is a Northern zonal tertiary facility which provides cervical screening clinic three times a week for general population, and Mawenzi Hospital is a Kilimanjaro regional hospital which provides cervical cancer screening two times a week. In Dar-es-Salaam, women from Ilala, Temeke, and Mwananyamala district were included while in the Kilimanjaro region, women originating from the urban and rural district of Moshi – including Hai and Rombo – were included. Originally, the study was designed as a double-site study (KCMC/ORCI), however, due to a slower-than-anticipated recruitment rate, a third study site (Mawenzi) was added six months into the enrolment period. Women were eligible for inclusion if they were 25-60 years and attended a patient-initiated routine cervical cancer screening at one of the study sites. Women were excluded if they were pregnant, on their menstrual period, had a history of premalignant lesions of the cervix within the last 12 months, had previously been diagnosed with cervical cancer or had undergone abdominal hysterectomy. Women on their menstrual period were encouraged to return once their menstrual period was over. Following a detailed explanation of the study, all participants provided written informed consent. Fingerprints were used for illiterate participants. The CONCEPT study was approved by the Ethical Committee of the Tanzanian National Institute of Medical Research (NIMR/HQ/R.8a/Vol.IX/1955), and is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement (online supplementary appendix 2). HIV-positive women were oversampled from Care and

Treatment Clinics (CTC) at the study sites from where they were referred to the screening clinics. The total number of women and HIV-positives required for the study was found through a power calculation based on McNemar's test comparing two diagnostic tests (S1: standard test (VIA) versus S2: new test (careHPV)). The power calculation was based on the research group's previous study in Tanzania[21]. It was estimated that 180-200 women would have precancerous lesions at baseline (~true positives) and assuming a significance level of 5% , 80% power, and a sensitivity of VIA of 30%, it would be possible to detect a significant difference if the sensitivity of the new test would be at least 44%. It was anticipated that *care*HPV testing would have a higher sensitivity than VIA.

Data were collected during the enrolment visit, at 14 months (1st follow-up), and at 28 months (2nd follow-up, ongoing). As there is no a predefined optimal duration of time to investigate the natural history of HPV, the length of follow-up was based on a number of factors, including the recommended duration of time between cervical cancer screenings for HIV-positive women (12 months)[33], available resources, risk for developing cervical lesions, and limiting the workload at the screening clinics by minimising overlaps between enrolment and follow-up visits. Healthcare providers working at the screening clinics enrolled participants and collected data following protocols developed specifically for the project. At inclusion, all participants were given a 14-months follow-up appointment written on an appointment card. If the women did not attend their follow-up visit within one month of their appointment, an active follow-up procedure was initiated. Firstly, non-attendees were contacted by phone and encouraged to attend (tracing method I). If the woman did not show up within two weeks of the phone call, the women had a home-visit by an outreach nurse who encouraged her to attend (tracing method II). If the woman still did not attend and consented to it, an outreach nurse visited her again and conducted the follow-up visit at home (tracing method III). Transportation costs were compensated for those women who were reminded to come. Women, who participated in the first follow-up were appointed a second follow-up visit 28 months after initial recruitment. If the woman did not attend the 2nd follow-up, tracing method I and III were re-initiated.

Assessment of exposure

At inclusion, socio-demographic, lifestyle, reproductive, and sexual characteristics were collected during a personal interview using a modified version of a standardised questionnaire adopted from a previous study conducted in Tanzania[34] (supplementary online appendix 3). The questionnaire was hardcopy, developed in English while the interview was conducted in Kiswahili with direct translation. A Kiswahili version of the questionnaire was available to guide the interviewers. A detailed contact information form was filled at enrolment and updated at follow-up. Participants were screened by trained healthcare providers according to the standard national cervical cancer screening prevention programme in Tanzania[35]. This entails a cost-free gynaecological examination with VIA, HIV-testing and HIV-counselling. Venous blood from the index finger was tested by use of a quick HIV-1/2 test (www.alere.com), and a supplementary quick HIV-1/2 test (Abbott Laboratories) was performed as confirmatory for positive results. Discordant results were further confirmed using Unigold (Trinity Biotech). Women who screened VIA-positive or were suspected of manifest cancer were managed on-site based on the National Cervical Cancer Service Delivery Guidelines. This included treatment with cryotherapy or loop electrosurgical excision procedure (LEEP) for VIA-positives, and punch biopsy and referral for treatment at the oncology clinic at ORCI for cancer suspicions[35]. Further, weight and height were measured and registered on a hard-copy registration sheet together with the HIV- and VIA-result (Table 1).

Table 1. Overview of data collected in the CONCEPT cohort

	Measurements	Instrument	Storage and analysis
Baseline 17 Aug 2015 – 6 Jul 2017	**Biological samples**		
	1 provider-collected cervical swab for: • *care*HPV® DNA-testing	• Aryes spatula • Kept in *care*HPV collection medium	• Samples stored on-site in laboratories at room temperature • When 90 samples were available they were processed on-site on a *care*HPV machine • Results registered on *care*HPV sheet and stored on-site
	1 provider-collected cervical swab for: • Cytology • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula • Kept in PreServCyt solution	• Samples stored on-site in laboratories at room temperature until enrolment had finished • Then the samples were sent to the Pathology Department at Lillebaelt Hospital, Denmark and processed on the

			ThinPrep5000 Autoloader Instrument, Hologic® for cytology • Remaining material of the samples were sent to the Section for Experimental Virology, Tubingen University, Germany and underwent HC2 DNA testing and genotyping using LiPaExtra • Cytology and HC2 and genotype results were sent to OUH, Denmark
	Venous blood from index finger for: • HIV-test	• Quick HIV-1/2 test	• Immediate results registered on registration form and stored on-site
	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• Immediate results registered on registration form and stored on-site
	Anthropometric measures • Weight • Height	• Scale and altitude meter	• Immediate results registered on registration form and stored on-site
	Personal interview • Socio-demographic factors • HIV treatment and CD4 count • Lifestyle factors • Sexual and reproductive factors	• Structured questionnaire	• Interviewed by nurse and stored on-site • CD4 count abstracted from CTC cards and further traced in patient files
14-months follow-up (1st) ***17 Oct 2016 – 6 Oct 2018***	**Biological samples** 1 provider-collected cervical swab *or* self-collected swab for: • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula (provider-based) • Evalyn® brush (self-swab) • Kept in PreServCyt solution	• Self-swabs were conducted in the women's home (cf. tracing method III) and transferred to the study sites where they were stored with ThinPrep samples similarly to baseline until 1st follow-up had finished • Then the samples were sent to the Section for Experimental Virology, Tubingen University, Germany and underwent HC2 DNA testing and genotyping using LiPaExtra • HC2 and genotype results were sent to OUH, Denmark
	Venous blood from index finger for: • HIV-test (if negative at baseline)	• Quick HIV-1/2 test	• Immediate results registered on registration form and stored on-site • HIV-test was not conducted on women who participated from home (cf. tracing method III)
	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• Immediate results registered on registration form and stored on-site • Not conducted on women who participated from home (cf. tracing method III)
	Personal interview • HIV treatment and CD4 count • Sexual factors	• Structured questionnaire	• Interviewed by nurse at clinic or at home and stored on-site • CD4 count abstracted from CTC cards and further traced in patient files
28-months follow-up (2nd) ***(17 December***	**Biological samples** 1 provider-collected cervical swab *or* self-swab only for HPV-positive women: • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula (provider-based) • Evalyn® brush (self-swab) • Kept in PreServCyt solution	• *Same procedure as in 1st follow-up*

	Venous blood from index finger for: • HIV-test (if negative at 1st follow-up)	• Quick HIV-1/2 test	• *Same procedure as in 1st follow-up*
	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• *Same procedure as in 1st follow-up*
	Personal interview • HIV treatment and CD4 count • Sexual factors	• Structured questionnaire	• *Same procedure as in 1st follow-up*

Prior to the routine VIA examination, cervical swabs were taken using (I) an Aryes spatula for *care*HPV test (www.qiagen.com), and another specimen was taken using (II) a ThinPrep® Pap Test Plastic Spatula for liquid-based cytology, HPV DNA testing and genotyping by use of HC2 and LiPaExtra (Innogenetics, Gent, Belgium). The cervical samples for *care*HPV analysis were kept in a *care*HPV collection medium and stored at room temperature (max 25°C) in laboratories at ORCI or KCMC. Once 90 samples had been collected, they were analysed for HR HPV using a *care*HPV machine. A test was considered positive if one or more of the following 14 HR HPV types were detected: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. The results were registered on a *care*HPV results sheet (Table 1).

The samples for HC2 testing, genotyping, and cytology were kept in a PreServCyt solution (Hologic, Inc. 250 Campus Drive Marlborough, MA 01752 USA) and stored at room temperature in laboratories at ORCI and KCMC. Once enrolment had finished, the PreServCyt vials were sent to the Department of Pathology at Lillebaelt Hospital, Vejle, Denmark and processed at the ThinPrep5000 Autoloader Instrument, Hologic® according to manufactures instruction and stained with ThinPrep Stain®. The slides were scanned by the Thin Prep Imaging System® with selection of 22 Fields of view which was reviewed by cytotechnologist in review scopes. The specimens were evaluated for adequacy and for abnormal cells. If abnormal cells were detected, the slides were consulted with a gynae-pathologist who made the final diagnosis. The specimens were diagnosed according to the Bethesda Nomenclature for System for Cervical Cytology 2014[36]into following categories: Negative for intra epithelial lesion (NILM), Atypical Squamous Cell of Undetermined

Significance (ASCUS), Atypical Squamous Cell in which High grade squamous intraepithelial lesion cannot be excluded (ASCH), Low grade Squamous Intraepithelial Lesion (LSIL), High grade Squamous Intraepithelial Lesion (HSIL), Atypical Glandular Cell (AGC), Adenocarcinoma In Situ(AIS), and Adenocarcinoma. The remaining material of the PreServCyt vials were sent to the Section for Experimental Virology, Tubingen University, Germany for HPV DNA testing and genotyping. HPV DNA testing was done using HC2 DNA test (www.qiagen.com) with a HR cocktail probe. A test was considered positive if one or more of the following 14 HR HPV types were found: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. A threshold of 1.0pg HPVDNA/ml, which corresponds to 1.0 relative light unit coefficient, was used, as recommended by United States Food and Drug Authority. HPV-positive samples were genotyped using LiPaExtra, which can detect 28 HPV types, 18 HR risk types (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and 10 low risk types (HPV 6, 11, 40, 43, 44, 54, 69, 70, 71, 74)[37].

Outcome measures

Women who attended their follow-up appointment at the screening clinics were HIV-tested (if negative at baseline), had a cervical swab collected with a ThinPrep® Pap Test Plastic Spatula – for HPV DNA testing by use of HC2 and genotyping by use of LiPaExtra – and underwent VIA (Table 1). Further, sexual and reproductive characteristics were updated by use of a structured questionnaire (online supplementary appendix 4). Women who did not attend their follow-up appointment at the clinic but consented to having a home-visit appointment (cf. tracing method III) responded to the questionnaire and had cervical specimens collected by use of an Evalyn self-sampling/self-swab device (www.roversmedicaldevices.com). The samples were transferred to laboratories at ORCI and KCMC where they were kept in a PreServCyt solution and stored at room temperature.

Data management

Questionnaires, registrations forms, contact forms, and *care*HPV result sheets were stored in different cabinets in locked offices at KCMC and ORCI, after which they were double entered into EpiData by data

clerks. Together with lab results these data were sent to the Research unit for Gynaecology& Obstetrics, Odense University Hospital (OUH), Odense, Denmark where they were merged and constructed into a baseline database. Data with invalid IDs or no data registered were excluded upon creation of the database. Similarly to baseline, follow-up data were sent to OUH after which it was merged with the baseline database. Follow-up IDs that could not match a baseline ID were excluded.

Patient and public involvement

Study participants were not involved in the design or recruitment of the study. In order to provide increase public awareness, government and religious leaders were informed about the project, the latter through mosques and churches. When the study finishes, the results and their potential implication to the public will be communicated through meetings with health authorities, policy briefings, and announcements in the mainstream media.

Findings to date

Baseline findings

A total of 4080 women were enrolled into the CONCEPT study. After inclusion, 37 study participants were excluded leaving the total cohort to consist of 4043 women (fig 1). The baseline distribution of the socio-demographic is presented in Table 2. A total of 718 women (17.8%) were HIV-positive and the majority of these were 35-39 years old (22.9%) while the majority of HIV-negative women were 40-44 years old (19.2%). Among the HIV-positives, 49.7% were married (n=356) whilst 73.6% of HIV-negatives were married (n=2434). Most of both HIV-positive (70.4%; n=504) and HIV-negative women (64.1%;n=2127) had completed primary school. More HIV-negative women (87.0%; n=2879) reported to have had sex within the last 12 months compared to HIV-positive women (72.7%; n=520), while more HIV-positives (26.2%) than HIV-negatives (9.8%) reported to have had used condoms at every intercourse. In relation to number of lifetime partners, 71.9% of HIV-positives reported having more than one lifetime partner whilst the

corresponding number for HIV-negative women was 61.0%. The CD4 count for HIV-positive women were as follows: 8.6% (n=62) reported having a CD4 count ≤199; 30.5% (n=219) had a CD4 ranging from 200-499; and 48.9% (n=347) had a CD4 count ≥500. Further, 12.5% (n=90) of the HIV-positives did not report the CD4 count.

Table 2: Selected socio-demographic, lifestyle, sexual and reproductive characteristics of the cohort at baseline and 1st follow-up stratified according to HIV-status

	COHORT PROFILE AT BASELINE						COHORT PROFILE AT 1ST FOLLOW-UP					
	Total (n=4043)		HIV-positive (n=718; 17.8%)		HIV-negative (n=3325, 82%)		Total (n=3074)		HIV-positive* (n=552; 18.0%)		HIV-negative* (n=2522; 82.0%)	
	N	%	N	%	N	%	N	%	N	%	N	%
Age												
25-29	527	13.0	43	6.0	484	14.6	344	11.2	26	4.7	318	12.6
30-34	599	14.8	78	10.9	521	15.7	432	14.1	61	11.1	371	14.7
35-39	744	18.4	164	22.9	580	17.5	547	17.8	121	21.9	426	16.9
40-44	787	19.5	149	20.8	638	19.2	634	20.6	115	20.8	519	20.6
45-49	667	16.5	138	19.2	529	15.9	522	17.0	112	20.3	410	16.7
50-60	716	17.7	145	20.2	571	17.2	595	19.4	117	21.2	478	18.9
Missing	3	0.1	1	0.14	2	0.06	-	-	-	-	-	-
Marital status												
Married	2790	69.0	356	49.7	2434	73.6	2159	70.2	288	52.2	1871	74.2
Cohabiting	58	1.4	14	2.0	44	1.3	44	1.4	11	2.0	33	1.3
Single	487	12.0	110	15.4	377	11.4	335	10.9	76	13.8	259	10.3
Divorced/widow	687	17.0	236	33.0	451	13.6	527	17.1	176	31.9	351	13.9
Missing	21	0.5	2	0.28	19	0.57	9	0.3	1	0.2	8	0.3
BMI												
Underweight	96	2.4	27	3.9	69	2.1	73	2.4	21	3.8	52	2.1
Normal	1149	28.4	269	38.5	880	27.3	839	27.3	199	36.1	640	25.4
Overweight	2190	54.2	334	47.8	1856	57.6	1695	55.1	259	46.9	1436	56.9
Obese	486	12.0	69	9.9	417	12.9	406	13.2	59	10.7	347	13.8
Missing	122	3.0	19	2.15	103	3.1	61	2.0	14	2.5	47	1.9
Education level												
No formal education	126	3.1	32	4.5	94	2.8	89	2.9	23	4.2	66	2.6
Primary	2631	65.1	504	70.4	2127	64.1	2027	65.9	381	69.0	2027	65.3
Secondary	882	21.8	146	20.4	736	22.2	672	21.9	123	22.3	672	21.8
College	396	9.8	34	4.7	362	10.9	280	9.1	23	4.2	280	10.2
Missing	8	0.2	2	0.28	6	0.18	6	0.2	2	0.4	6	0.7
Religion												
Christian	2708	67.0	505	70.6	2203	66.8	2064	67.1	391	70.8	1673	66.3
Muslim	1289	31.9	206	28.8	1083	32.8	978	31.8	155	28.1	823	32.6
Other	16	0.4	4	0.6	12	0.4	13	0.4	4	0.7	9	0.4
Missing	30	0.7	3	0.42	27	0.81	19	0.6	2	0.7	17	0.6
No of living children												
0	35	0.9	5	0.7	30	0.9	22	0.7	4	0.7	18	0.7
1-2	1506	37.2	295	41.8	1211	37.5	1112	36.2	219	39.7	893	35.4
3	901	22.3	180	25.5	721	22.3	729	23.7	141	25.5	588	23.2
4-6	1135	28.1	183	25.9	952	29.5	900	29.3	150	27.2	750	29.7
>7	139	3.4	19	2.7	120	3.7	99	3.2	12	2.2	87	3.5
Never been pregnant	221	5.5	24	3.4	197	6.1	144	4.7	16	2.9	128	5.1
Missing	106	2.6	12	1.67	94	2.83	68	2.2	10	1.8	58	2.3

Years living with partner															
0-1	166	4.1		21	3.0		145	4.4		102	3.3		18	3.3		84	3.3
2-4	517	12.8		112	15.9		405	12.4		355	11.6		74	13.4		281	11.4
5-9	723	17.9		143	20.3		580	17.8		515	16.8		106	19.2		409	16.2
10-14	648	16.0		125	17.7		523	16.0		502	16.3		97	17.6		405	16.1
15-19	546	13.5		104	14.8		442	13.6		443	14.4		85	15.4		358	14.2
>20	1203	29.8		162	23.0		1041	31.9		993	32.2		137	24.8		856	33.9
Single with no regular partner	163	4.0		38	5.4		125	3.8		118	3.8		27	4.9		91	3.6
Missing	77	1.9		13	1.81		64	1.92		46	1.5		8	1.5		38	1.5
Sex in last 1 year															
Yes	3399	84.1		520	72.7		2879	87.0		2583	84.0		404	73.2		2179	86.4
No	610	15.1		195	27.3		415	12.5		478	15.6		146	26.5		332	13.2
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	20	0.5		3	0.42		17	0.51		8	0.3		2	0.4		6	0.2
Condom use within last 12 months															
No sex within last 12 months	610	15.1		195	27.3		415	12.6		478	15.6		146	26.5		332	13.2
At every intercourse	509	12.6		187	26.2		322	9.8		381	12.4		139	25.2		242	9.6
Rarely	204	5.0		29	4.1		175	5.3		146	4.8		25	4.5		121	4.8
No condom use	2678	66.2		303	42.4		2375	71.9		2052	66.8		239	43,3		1813	71.9
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	28	0.7		4	0.56		24	0.72		12	0.4		3	0.5		9	0.4
Number of lifetime partners															
1	1476	36.5		197	28.1		1279	39.0		1129	36.7		158	28.6		971	38.5
2	1053	26.0		194	27.7		859	26.2		819	26.6		155	28.1		664	26.3
3	709	17.5		147	21.0		562	17.1		516	16.8		101	18.2		415	16.5
4	284	7.0		60	8.6		224	6.8		221	7.2		46	8.3		175	6.8
5-8	329	8.1		65	9.3		264	8.1		255	8.3		49	8.9		206	8.2
>9	113	2.8		38	5.4		75	2.3		89	2.9		33	6.0		56	2.2
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	65	1.6		17	2.4		48	1.4		40	1.3		10	1.8		30	1.2

**According to HIV-status at baseline*

Among the 4043 participants , the cervical sample was insufficient for HPV analysis for 396 women (9.8%) at baseline, leaving 3667 women eligible for analysis of HPV-positivity. Further, 27 women (0.5%) did not have a sample for cervical cytology, leaving 4116 women available for cytological analysis of cervical lesions. All 4043 women were either tested for HIV or had previously tested HIV-positive. At baseline, 696 women (17.2%) tested HR HPV-positive by HC2. The cytology showed that overall 3.4% (n=139) had HSIL+ whilst 8.1% (n=329) of women had LSIL.

1st follow-up findings

A total of 3805 women (94%) were eligible for 1st follow-up – 238 women (6%) were ineligible due to becoming pregnant, having moved, having had a hysterectomy or having become sick or died (fig 1).Of the 3805 women, 3074 women(81%) attended the first follow-up visit approximately 14th months after enrolment. However, among the attendees only 500 (16%) attended within in 30 days of their scheduled appointment date and without being traced for follow-up. A total of 1088(35%) attended the clinic after a phone call reminder(tracing method I), 62 women (2%) attended the clinic after a nurse home-visit(tracing method II), whilst 1253 women (41%) were followed up at home and had specimens collected using self-sampling device (tracing method III).A total of 731 women (19%) were lost to follow-up (fig 1).

(Fig 1: Flow chart of enrolment and follow-up of CONCEPT cohort)

The women who participated in the 1st follow-up were very similar to those who did not attend when looking at socio-demographic factors (table 2). However, overall fewer women were HR HPV-positive at follow-up compared to baseline (14.8% vs. 17.2%), and fewer HIV-positive women were HR HPV-positive at follow-up compared to baseline (24.1% vs. 31.6%) (table 3).

Table 3. HR HPV, HIV, and cytology results at baseline and 1st follow-up

	Baseline				First follow up		
	Total(N=4043)				Total(N=3074)		
HPV	**n**	**%**	**(95% CI)**		**n**	**%**	**(95% CI)**
Positive	696	17.2	(0.16-0.18)		438	14.3	(0.13-0.16)
Negative	2951	73	(0.72-0.74)		2595	84.4	(0.83-0.86)
Missing	396	9.8	(0.09-0.1)		41	1.3	(0.01-0.02)
HIV							
Positive	718	17.8	(0.17-0.19)		552	18	(0.17-0.2)
Negative	3325	82.2	(0.81-0.83)		2522	82	(0.80-0.83)
Cytology							
HSIL	139	3.4	(0.03-0.04)				

LSIL	329	8.1	(0.07-0.09)		
Negative	3548	87.8	(0.87-0.89)		
Missing	27	0.7	(0.00-0.01)		

Strengths and Limitations

This is a large-scale longitudinal cervical cancer study conducted in an HIV endemic population that aims to address a major cause of disease among East-African women, which so far has not received much focus within global health research. Women are followed over a long duration of time and with a large amount of data being collected by use of questionnaires and lab tests. Given the nature of our study a significant attrition rate was expected. However, with the carefully designed tracing plans and dedicated home-visiting staff we managed to attain an 81% participation rate at 1st follow-up. As women were enrolled during a patient-initiated screening at screening clinics, detailed HIV documentation was challenging to obtain as CTC cards were poorly documented or had not been brought to the screening. Despite the nurses calling these women after enrolment to retrieve the information, it was not provided by many HIV-positive participants. This has led to a certain amount of missing values for a few variables and have limited our ability and power in analyses involving HIV immunologic markers and treatment.

Future plans

A second follow-up is underway (17 December 2018 – primo October 2020). Based on our large-scale data of both HPV infection in general and type specific characterised by the women's HIV-status, we plan to integrate this data with a previous cross-sectional HPV study (PROTECT Study) conducted in this population as this can increase power in our findings. As we have already established a large cohort of participants, we foresee a potential to further characterise the HPV burden and establish risk factors over a longer course of time. Specifically, we wish to compare the clinical performance of three potential cervical

cancer screening strategies in Tanzania, namely (I) HC2 testing at varying cut-points of viral load as measured by the RLU value; (II) HC2 testing with VIA triage; and (III) HC2 testing with triage using HPV16/18 genotyping. Further, we also foresee the possibility of linking our evidence with other groups in this population including males, adolescents, and pregnant women. This may provide additional information on the similarities of epidemiological burden among these group and delineate differences in the correlations of HPV and HPV-related disease across these different groups.

Collaboration

Researchers interested in collaboration in this discipline especially in East and Central Africa are welcomed. This may be in extracting data from the project, jointly requesting further investigation from the cohort.

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Contributors

JM, RM, VR, and SKK designed the CONCEPT study. JM, RM, VR, SKK, JK, PS, CK, BM, and DSL were

involved in collecting data for the study. CW, SKK, VR, BM, and DSL, were involved in data analysis and interpretation. CW, BM, DSL contributed to the conception of this article, and CW, BM, DSL, PS, JK, CK, VR, JM, SKK, and RM were involved in the manuscript writing and revision. All authors read and approved the final manuscript.

Data sharing statement

Data collected for the CONCEPT cohort study are available upon request. Individual participant data will de-identified. Additional available data include the CONCEPT eligibility and informed consent form, the CONCEPT contact information form, the protocol for how to deliver HPV-positive results to participants, the protocol for how to trace non-attendants. Data will be made available upon request by contacting the first or last author of this study by email at barikimchome@gmail.com/dsondergaard@health.sdu.dk, who will then seek approval by the primary investigator in the CONCEPT project, Julius D. Mwaiselage.

Competing interests

There are no competing interests for any author.

Supplementary material

Supplementary appendix 1	Original protocol for CONCEPT study
Supplementary appendix 2	STROBE checklist
Supplementary appendix 3	CONCEPT baseline questionnaire
Supplementary appendix 4	CONCEPT 1st follow-up questionnaire

Abbreviations

ACCME	African Collaborative Center for Microbiome and Genomics Research

AGC	Atypical glandular cell
AIS	Adenocarcinoma in situ
ASCUS	Atypical squamous cell of undetermined significance
ASCH	Atypical squamous cell in which High grade squamous intraepithelial lesion cannot be excluded
CTC	Care and treatment clinic
CONCEPT	Comprehensive Cervical Cancer Prevention in Tanzania
Danida	Danish International Development Agency
HARP	HPV in Africa Research Partnership
HC2	Hybrid Capture 2
HIC	High-income countries
HIV	Human immuno-deficiency virus
HPV	Human papilloma virus
HSIL	High grade squamous intraepithelial lesion
KCMC	Kilimanjaro Christian Medical Centre
LEEP	Loop electrosurgical procedure
LMIC	Low- and middle-income countries
LSIL	Low grade squamous intraepithelial lesion
NILM	Negative for intra epithelial lesion
PROTECT	Prevention of Cervical Cancer in Tanzania
ORCI	Ocean Road Cancer Institute

Figure legends

Figure 1	Flow chart of enrolment and follow-up of CONCEPT cohort

References

1. World Health Organization. Improving data for decision-making: a toolkit for cervical cancer prevention and control programmes. 2018. http://apps.who.int/iris.
2. Serrano B, Brotons M, Bosch FX, et al. Epidemiology and burden of HPV-related disease. *Best Pract Res Clin Obstet Gynaecol* 2018;47:14-26. doi: 10.1016/j.bpobgyn.2017.08.006 [published Online First: 2017/10/19]
3. Torre LA, Islami F, Siegel RL, et al. Global Cancer in Women: Burden and Trends. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2017;26(4):444-57. doi: 10.1158/1055-9965.epi-16-0858 [published Online First: 2017/02/23]
4. Bruni LB-RL AG, Serrano B. Human Papillomavirus and Related Diseases in Tanzania. Summary Report. *ICO Information Centre on HPV and Cancer (HPV Information Centre)* 2016; 15
5. Dartell MA, Rasch V, Iftner T, et al. Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative Tanzanian women. *International journal of cancer* 2014;135(4):896-904. doi: 10.1002/ijc.28712 [published Online First: 2014/01/07]
6. Linde DS, Korsholm M, Katanga J, et al. One-way SMS and healthcare outcomes in Africa: Systematic review of randomised trials with meta-analysis. *PloS one* 2019;14(6):e0217485. doi: 10.1371/journal.pone.0217485 [published Online First: 2019/06/07]
7. Gard AC, Soliman AS, Ngoma T, et al. Most women diagnosed with cervical cancer by a visual screening program in Tanzania completed treatment: evidence from a retrospective cohort study. *BMC public health* 2014;14:910. doi: 10.1186/1471-2458-14-910 [published Online First: 2014/09/05]
8. Bruni L, Diaz M, Castellsague X, et al. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *The Journal of infectious diseases* 2010;202(12):1789-99. doi: 10.1086/657321 [published Online First: 2010/11/12]
9. Nowak RG, Gravitt PE, Morrison CS, et al. Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe. *J Infect Dis* 2011;203(8):1182-91. doi: 10.1093/infdis/jiq172 [published Online First: 2011/04/01]
10. Dames DN, Blackman E, Butler R, et al. High-risk cervical human papillomavirus infections among human immunodeficiency virus-positive women in the Bahamas. *PloS one* 2014;9(1):e85429. doi: 10.1371/journal.pone.0085429 [published Online First: 2014/01/28]
11. Looker KJ, Ronn MM, Brock PM, et al. Evidence of synergistic relationships between HIV and Human Papillomavirus (HPV): systematic reviews and meta-analyses of longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status. *Journal of the International AIDS Society* 2018;21(6):e25110. doi: 10.1002/jia2.25110 [published Online First: 2018/06/07]
12. Akarolo-Anthony SN, Famooto AO, Dareng EO, et al. Age-specific prevalence of human papilloma virus infection among Nigerian women. *BMC public health* 2014;14:656. doi: 10.1186/1471-2458-14-656 [published Online First: 2014/06/29]
13. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *International journal of cancer* 2012;131(10):2349-59. doi: 10.1002/ijc.27485 [published Online First: 2012/02/11]
14. Edna Omar V, Orvalho A, Nalia I, et al. Human papillomavirus prevalence and genotype distribution among young women and men in Maputo city, Mozambique. *BMJ open* 2017;7(7):e015653. doi: 10.1136/bmjopen-2016-015653 [published Online First: 2017/07/19]
15. Husain RS, Ramakrishnan V. Global Variation of Human Papillomavirus Genotypes and Selected Genes Involved in Cervical Malignancies. *Annals of global health* 2015;81(5):675-83. doi: 10.1016/j.aogh.2015.08.026 [published Online First: 2016/04/03]
16. Ogembo RK, Gona PN, Seymour AJ, et al. Prevalence of human papillomavirus genotypes among African women with normal cervical cytology and neoplasia: a systematic review and meta-analysis. *PloS one* 2015;10(4):e0122488. doi: 10.1371/journal.pone.0122488 [published Online First: 2015/04/16]
17. World Health Organization. Human papillomavirus (HPV) and cervical cancer. 2019. https://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer.
18. Bosch FX, Munoz N. The viral etiology of cervical cancer. *Virus research* 2002;89(2):183-90. [published Online First: 2002/11/26]

19. Kelly HA, Ngou J, Chikandiwa A, et al. Associations of Human Papillomavirus (HPV) genotypes with high-grade cervical neoplasia (CIN2+) in a cohort of women living with HIV in Burkina Faso and South Africa. *PloS one* 2017;12(3):e0174117. doi: 10.1371/journal.pone.0174117 [published Online First: 2017/03/24]
20. Adebamowo SN, Dareng EO, Famooto AO, et al. Cohort Profile: African Collaborative Center for Microbiome and Genomics Research's (ACCME's) Human Papillomavirus (HPV) and Cervical Cancer Study. *International journal of epidemiology* 2017;46(6):1745-45j. doi: 10.1093/ije/dyx050 [published Online First: 2017/04/19]
21. Dartell M, Rasch V, Kahesa C, et al. Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study. *Sexually transmitted diseases* 2012;39(3):201-8. doi: 10.1097/OLQ.0b013e31823b50ad [published Online First: 2012/02/18]
22. Watson-Jones D, Baisley K, Brown J, et al. High prevalence and incidence of human papillomavirus in a cohort of healthy young African female subjects. *Sexually transmitted infections* 2013;89(5):358-65. doi: 10.1136/sextrans-2012-050685 [published Online First: 2013/03/15]
23. Houlihan CF, Baisley K, Bravo IG, et al. Rapid acquisition of HPV around the time of sexual debut in adolescent girls in Tanzania. *Int J Epidemiol* 2016;45(3):762-73. doi: 10.1093/ije/dyv367 [published Online First: 2016/03/06]
24. Baisley KJ, Andreasen A, Irani J, et al. HPV prevalence around the time of sexual debut in adolescent girls in Tanzania. *Sex Transm Infect* 2019 doi: 10.1136/sextrans-2019-054012 [published Online First: 2019/06/22]
25. Linde DS, Andersen MS, Mwaiselage JD, et al. Text messages to increase attendance to follow-up cervical cancer screening appointments among HPV-positive Tanzanian women (Connected2Care): study protocol for a randomised controlled trial. *Trials* 2017;18(1):555. doi: 10.1186/s13063-017-2215-x [published Online First: 2017/11/23]
26. Linde DS, Rasch V, Mwaiselage JD, et al. Competing needs: a qualitative study of cervical cancer screening attendance among HPV-positive women in Tanzania. *BMJ open* 2019;9(2):e024011. doi: 10.1136/bmjopen-2018-024011 [published Online First: 2019/03/02]
27. Linde DS AM, Mwaiselage JD, Manongi R, Kjaer SK, Rasch V. One-way text messages versus no text messages on attendance to follow-up cervical cancer screening among HPV-positive Tanzanian Women (Connected2Care): a parallel-group randomized controlled trial. *JMIR Preprints* 15/08/2019:15863 doi: DOI: 10.2196/preprints.15863
28. Koliopoulos G, Nyaga VN, Santesso N, et al. Cytology versus HPV testing for cervical cancer screening in the general population. *The Cochrane database of systematic reviews* 2017;8:Cd008587. doi: 10.1002/14651858.CD008587.pub2 [published Online First: 2017/08/11]
29. Bakiewicz A, Rasch V, Mwaiselage J, et al. "The best thing is that you are doing it for yourself" - perspectives on acceptability and feasibility of HPV self-sampling among cervical cancer screening clients in Tanzania: a qualitative pilot study. *BMC women's health* 2020;20(1):65. doi: 10.1186/s12905-020-00917-7 [published Online First: 2020/04/03]
30. Katanga J, Kjaer SK, Manongi R, et al. Performance of careHPV, hybrid capture 2 and visual inspection with acetic acid for detection of high-grade cervical lesion in Tanzania: A cross-sectional study. *PloS one* 2019;14(6):e0218559. doi: 10.1371/journal.pone.0218559 [published Online First: 2019/06/20]
31. Linde DS, Andersen MS, Mwaiselage J, et al. Effectiveness of One-Way Text Messaging on Attendance to Follow-Up Cervical Cancer Screening Among Human Papillomavirus-Positive Tanzanian Women (Connected2Care): Parallel-Group Randomized Controlled Trial. *Journal of medical Internet research* 2020;22(4):e15863. doi: 10.2196/15863 [published Online First: 2020/04/03]
32. McHome BL, Kjaer SK, Manongi R, et al. HPV types, cervical high-grade lesions and risk factors for oncogenic human papillomavirus infection among 3416 Tanzanian women. *Sex Transm Infect* 2020 doi: 10.1136/sextrans-2019-054263 [published Online First: 2020/04/10]
33. Cervical cancer prevention guidelines for low-resource settings. Available: http://resources.jhpiego.org/system/files/resources/cecap_trainer_0.pdf. 2011
34. Dartell M, Rasch V, Munk C, et al. Risk factors for high-risk human papillomavirus detection among HIV-negative and HIV-positive women from Tanzania. *Sexually transmitted diseases* 2013;40(9):737-43. doi: 10.1097/olq.0000000000000005 [published Online First: 2013/08/21]
35. Paul D. Blumenthal NM. Cervical Cancer Prevention Guidelines for Low-Resource Settings 2007: Jhpiego; 2005 [Available from: http://reprolineplus.org/system/files/resources/CeCaPfullmanual.pdf.
36. Nayar R, Wilbur DC. The Pap Test and Bethesda 2014. "The reports of my demise have been greatly exaggerated." (after a quotation from Mark Twain). *Acta Cytol* 2015;59(2):121-32. doi: 10.1159/000381842 [published Online First: 2015/05/23]
37. Xu L, Padalko E, Ostrbenk A, et al. Clinical Evaluation of INNO-LiPA HPV Genotyping EXTRA II Assay Using the VALGENT Framework. *Int J Mol Sci* 2018;19(9) doi: 10.3390/ijms19092704 [published Online First: 2018/09/14]

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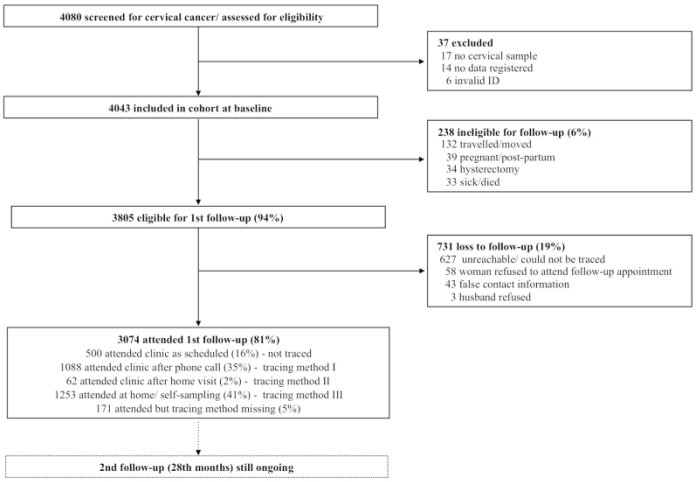

Flow chart

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Appendix A: Project Description

Comprehensive Cervical Cancer Prevention in Tanzania (CONCEPT)

1. Project Summary

The natural history of Human papillomavirus (HPV) in sub-Saharan Africa is not yet fully understood. As persistent HPV infection is a necessary factor in development of cervical cancer – a major health problem in sub-Saharan Africa - information about how HIV together with other risk factors interacts with HPV acquisitionand HPV persistence/clearance is warranted. Additionally, concern prevails about the quality of cervical cancer preventive strategies in sub-Saharan Africa. Against this background the project aims to provide a better understanding of the natural history of HPV with a view to HIV status, to measure the impact of a novel and simple screening method based on *Care*HPV testing and to assess how continuity of care among women who are tested HPV positive can be improved. The study will be linked up with the existing cervical cancer screening program at Ocean Road Cancer Institute (ORCI) and Kilimanjaro Christian Medical Centre (KCMC); and will include 4000 women who are attending screening service or HIV care and treatment. HPV acquisition and persistence/clearance patterns as well as the absolute risk of severe cervical precancerous lesions will be determined through a follow up study lasting 28 months. The test performance of *Care*HPV testing, liquid-based cytology and VIA will be described and the operating characteristics of the three screening methods will be assessed according to HIV status. Finally, the impact of a mobile phone intervention and a patient navigation model will be assessed and compared according to the proportion of HPV positive women who return for follow-up examinations. Additionally, the project will implement a research capacity building component focusing on transfer of knowledge and technology as well as training of PhD students. The activities will be carried out as five sub-studies: i) HPV acquisition pattern; ii) HPV persistence/clearance pattern; iii) Test performance of *Care*HPVtesting, liquid-based cytology and VIA; iv) Continuity of care among screened positive women and v) research capacity building as well as transfer of knowledge and technology

2. Objectives

With the overall aim of substantially improving cervical cancer prevention in Tanzania and thereby reduce mortality, the CONCEPT project focuses onthe natural history of human papillomavirus (HPV), which is the most important risk factor for cervical cancer.

HPV can take the form of being either a transient infection, that relatively rapidly is cleared by the host immune system or it can becomea persistent infection that may progress to high-grade cervical lesions or cervical cancer**(Fig. 1)**.In spite of the fact that cervical cancer is the most common malignancy among women in Sub-Saharan Africa (1), little is known about the distribution of HPV types, risk factors of incidence and patterns of persistence for different HPV types. The proposed project will address this lack of knowledge and provide new information about the natural history of HPV and consequences of HPV infection among HIV positive and HIV negative women.In addition, there is concern about the performance of the screening approaches applied in many sub-Saharan African countries and information on the quality of novel, affordable screening approaches that will perform well in remote areas iswarranted. Finally, in many sub-Saharan African settingsworries prevail about lack of continuity of care among women who are diagnosed with precancerous lesionsand therefor relevant treatment is not always offered. The proposed project will address these shortcomings in cervical cancer prevention. The researchwill build on the resultspreviously obtained by our research team(2-6) and will be innovative in the way that it through a comprehensive approach will use thenatural history of HPV to identify opportunities to strengthening and further develop the existing screening program in Tanzania, with a particular view to the importance of HIV positivity. In addition, with the aim to bridge the gap in continuity of care among women diagnosed with precancerous lesions,the project will develop and test a reliable and sustainable communication system through a multidisciplinary approach, involving community education, social mobilization and use of cell-phones. Thus the proposed study has the potential to produce results with immediate public health impact.

The specific objectives of the project are:

1. To assess acquisition patterns and incidence of HPV infection with a specific focus on differences in HPV acquisition, distribution of HPV types and risk factors among HIV positive and HIV negative women

2. To assess persistence of high-risk HPV infection with a specific focus on whether there are differences in HPV persistence in relation to specific HPV types and differences in risk factors for HPV persistence among HIV positive and HIV negative women. In addition, it is the aim to examine the absolute risk of HSIL or worse in relation to both one time HPV positivity and HPV persistence while taking HIV status into account

3. To evaluate the performance ofSelf collected *Care*HPV testing, health provider collected HPV test, Pap smear (liquid-based cytology) and visual inspection with acetic acid (VIA) for detection of cervical precancerous lesions with a special view to test performance among HIV positive and HIV negative women.

4. To evaluate and compare two different interventions aiming at ensuring continuity of care among women who are tested HPV positive in terms of effect and costs, and to describe barriers for not adhering to the scheduled follow-up

5. To enhance research capacity and transfer of knowledge and technologythrough the training of PhD students and the involvement of a post-doctoral fellow

3. Project's methodology

Based on the experience and success of our previous study of HPV prevalence in Tanzanian women, the present study will be linked up with the existing cervical cancer screening program in Dar es Salaam and Kilimanjaro Region. To make sure that we will include enough HIV positive women into the study, we will oversample HIV positive women. This will be done through enrolment of women attending HIV care and treatment in the two study areas.A total of 4000 women will be enrolled at baseline in the study -3500 women from the two screening settings and 500 HIV positive women from two HIV care and treatment clinics. Based on our previous experience, amongthe 3500 women recruited from the screening settings, around 700 will be high-risk (HR)-HPV positive and nearly 350 women will be HIV positive(2). Among the 500 HIV positive women recruited from the HIV clinics, an estimated 250 women will beHPV positive(2). Hence, the total study sample of 4000 women will include an estimated 950 HPV positive and 850 HIV positive women.A power calculation was based on McNemars test in the situation where we compare two diagnostic tests (1: standard test (VIA)vs 2:new test (*Care*HPV)) where the outcome is sensitivity S_1 and S_2, respectively.Based on our previous studies in Tanzania (4) it is estimated that 180-200 women will have precancerous lesions at baseline (~true positive), and we assume a significance level of 5% and that the sensitivity of the standard test is S_1=30%. We will then with 80% power be able to detect a significant difference if the sensitivity of the new test is at least S_2=44%. As we anticipate *Care*HPV testing to have a much higher sensitivity, we will have sufficient power in the present study

An overview of the study design is outlined in **Fig. 2.** In principle the study comprises a baseline visit and 2 follow-up visits:

*At **baseline*** we will collect on all participating women a cervical sample for *Care*HPV testing, a novel and simple quick test for detection of HPV.We will also obtaina liquid-based cervical swab (ThinPrep) for cytology examination (subsequently prepared and diagnosedin Denmark), high-risk Hybrid Capture (HC2) testing (in Germany), and genotyping (PCR-based HPV testing in Germany). Following this, VIA will be done with 5% acetic acid. The Tanzanian staff will receive training (re-training) in sample collection and VIA before start of the study by national trainers according to IARC guidelines. In case of a positive cytology (HSIL or worse) the woman will be called in and will be treated according to the cervical cancer screening standard of care methods in Tanzania. Similarly, all VIA positive women will be treated according to the cervical cancer screening standard of care methods in Tanzania.Information on socio-economic characteristics, lifestyle factors and reproductive history will be recorded through a personal

interview, and blood samples for HIV testing will be obtained. Before the initiation of the study, the staff in Tanzania will receive training in *Care*HPV testing.The C*are*HPV (including currently known HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) will be tested within 14 days in Tanzania. At the ***first follow-up*****,** taking place 14 months after inclusion,a randomly selected sample of 500 women will be trained on self-collection of a cervical swab for HPV testing. Thereafter another cervical swab (ThinPrep) will be collected (on all study subjects in the 1st follow-up) by a trained health provider. At the ***second follow-up*****,** taking place 26 months after inclusion, a cervical swab (ThinPrep) will be obtained from each woman. Women who do not return to the clinic for first and second follow-up will be traced and visited at home and invited to attend the clinic for screening. If they do not wish to re-attend, they will be offered screening through a self-collected HPV sample.We anticipate a response rate in the 1st follow-up at 90% and a response rate in the 2nd follow-up at 80%. The anticipated follow-up rate is based on experiencesfrom previous follow-up studies in Tanzania(7).
The study is grouped in five work package according to the specific objectives:

Work package 1, Acquisition patterns of high-risk (HR) human papillomavirus (HPV) with a special view to HIV status: Among women testing HR-HPV negative at baseline (Fig. 2), all women testing HIV positive (~190 from the screening clinic and 250 from HIV clinics = 440 in total) as well a random sample of 560 HPV negative/HIV negative women will be invited to a new gynecological examination after 14 months (1st follow-up visit), where a health provider cervical swab (ThinPrep) sample on all women is taken.These sampleswill all be tested for HPV using HC2 and genotyping will be performed on the HPV positive samples. At the 2nd follow-up visit (at 26 months) a health provider taken cervical swab (ThinPrep) will be obtained. All samples from the 2nd follow-up will be sent to Denmark for establishment of a cytology diagnosis and the remaining material will be sent to Germany for HC2 testing and subsequent genotyping of the HPV positives.All cytology results and HPV results will be sent back to Tanzania. In case of a positive cytology (HSIL or worse) the woman will be called in and will be treated according to the cervical cancer screening standard of care methods in Tanzania.
Based on the literature (8) we estimate an HPV acquisition rate among the initially HPV negative women at 1st follow-up of around 10%, similarly an acquisition rare of 10% from the 1st to the 2nd follow-up. The association between HR-HPV acquisition and the women's age, life style characteristics, reproductive history and HIV status will be assessed.

Work package 2, Persistence patterns of high-risk HPV types and absolute risk of severe cervical lesions focusing on the importance of HIV status: Persistence/clearance patterns of HR-HPV will be determined among all women who are HR-HPV positive at baseline(Fig. 2) (~700 from the screening clinic and 250 from the HIV clinic i.e. ~950 in total). They will be invited for follow-up examinations and tested for HR-HPV after 14 and 26 months (1st and 2nd follow-up visit). For this group of women also a self-collected cervical swab will be obtained at the 1st follow-up in 500 randomly selected women. HPV genotyping will be performed among women who are HR-HPV positive during follow-up.Women who are persistently HPV positive for the same HPV type at enrolment and at 1st follow-up will be called in for a cytological examination at the respective clinic.Also in case of a positive cytology (HSIL or worse), the women will be called in for further follow-up. HR-HPV persistence/clearance patterns will be described in relation to the women's age, life style characteristics, reproductive history, HIV status and HPV genotype. We estimate a persistence rate of 40% after 14 months and of 20% after 26 months (9). Due to the fact that a cytology diagnosis is obtained on all women at the 2nd follow-up, we will also be able to look at the absolute risk of HSIL or worse in relation to both one time HPV positivity, HPV persistence and according to HIV status.

Work package 3, Test performance of *Care*HPV testing, pap smear and VIA for detection of cervical precancerous lesions: As described above, all 4000 women enrolled will be screened by use of *Care*HPV testing, Pap smear (liquid based cytology i.e. ThinPrep) and VIA at the study baseline, and the sensitivity and specificity of *Care*HPV testing and VIA will be estimated and the positive and negative predictive values calculated. The operating

characteristics of the two screening methods will be assessed according to HIV status. All VIA positive women will subsequently be treated in agreement with thecervical cancer screening standard of care methods in Tanzania. In case of a positive cytology that was not already identified through a positive VIA, the women will be called in for further follow-up.High-quality cervical liquid-based cytology and where possible also cervical biopsies will be used as Gold Standard. Based on the samples collected at the 1st follow-up, the HPV results from the self-collected brush and the health provider collected brush will be compared.

Work package 4, Continuity of care among women who are tested are HPV positive – a comparison of two different interventions: Women who are tested HPV positive at enrolment will be randomized to either a patient navigation model or a cell phone model consisting of automated SMS messages. *Patient navigation model*: A trained community health worker will be identified as the woman's patient navigator. There will be established a one-to-one relationship between the patient navigator and the woman to address anticipated barriers such as communication difficulties and difficulties with arranging transportation. *Cell phone model***:** HPV positive women will receive automatically generated SMS messages, which will convey HPV result, send appointment reminders and health information during the first 12-14 months follow-up period.After 20 months, the continuity of care, based on the number of HPV positive women who return for the 1st follow-up examination after 14 months, will be compared. Additionally, the average time spent providing navigation from an HPV positive result is established to 12-14 months after and the associated cost will be calculated. Likewise the price of establishing and maintaining the system generating the SMS reminders will be measured. The differences in total costs and re-attendance between patient navigation and SMS reminders will be calculated. Re-attendance will be defined as HPV positive woman who re-attend within 12-14 months after the HPV positive result is established. Finally**,** HPV positive women who do not re-attend for screening after 12-14 months will be traced and interviewed. A mixed method approach, relying on structured questionnaires, in-depth interview and key informant interviews will be used to describe perceived barriers for attending 12-14 months follow-up.

Work package 5, Health service capacity building for cervical cancer prevention:Health service capacity building will be performed at primary, secondary and tertiary level. At the primary and secondary levels, key barriers for optimal use of existing communication paths for ensuring continuity of care among women diagnosed with precancerous lesions will be identified through a register based desk study. Based on the results, interview guides will be developed for in-depth interviews with health providers working at primary and secondary level and community representatives. The experiences from this assessment will be used to develop a training program in cervical cancer prevention and patient navigation that will include staff at primary and secondary health units together with community health workers in Dar es Salaam and Kilimanjaro Region. The trained community health worker will be employed as patient navigators. At tertiary level, the project will respond to the research needs set forth by ORCI and KCMC. Three PhD courses, one in Clinical Trials, one in Prevention and Control of Gynaecological Cancers and one in Policy Brief Writing will be offered at KCMC in alignment with the exiting BSU initiatives at KCMC. The PhD courses will be co-developed and co-taught by Tanzanian and Danish researchers. At both ORCI and KCMC there is a need to strengthen the capacities of researchers to undertake in-country PhD training at an international level. To address this need, four PhD studies, three Tanzanian and one Danish (co funded by SDU), will be included in the project. The Tanzanian PhD students will be recruited through public announcement of the scholarships and competitive applications.Two of the Tanzanian PhD students will be enrolled at KCMC and one at ORCI. Theywill additionally conduct 3 months of academic work each year in Denmark. The project will be performed as a twinning arrangement where the Tanzanian and the Danish PhD students will work closely together. To increase the expertise within HPV epidemiology and HPV testing in Tanzania and thereby increase the sustainability of the project outcomes, a post-doctoral fellow, Crispin Kahesa(CK), who has obtained his PhD as part of our previous research (2-6, 9) and who is presently acting as national trainer for the cervical cancer

prevention program in Tanzania, will be employed in the project. He will be visiting Institute of Medical Virology at Tuebingen University in Germany to get detailed knowledge about HPV testing and HPV analyses. In addition, to enhance local expertise in cervical cancer screening and HPV testing, a faculty exchange to the International Agency for Research on Cancer (IARC) in Lyon will also be arranged. Finally, to further upgrade CK's academic skills he will be involved as a co-supervisor of the two PhD projects focusing on Cervical Cancer Screening and Continuity of Care and write two independent papers based on the research findings.

Ethical research permissions will be obtained from the Ministry of Health in Tanzania and from local authorities in Dar es Salaam and Kilimanjaro. Ethical clearance will be obtained from the Ethical Review Board at KCMC and ORCI as well as from the Ethical Review Board of the National Institute of Medical Research. The project will follow the international ethical guidelines developed by CIOMS (Council for International Organization of Medical Sciences), placing particularemphasis on ensuring participant safety. Hence, women who have a positive cytology (HSIL or worse) will be called in and treated according to Tanzanian standard of care. Similarly, women who are persistently HPV positive will be traced, and liquid-based cytology samples will be obtained and analyzed. In case of a positive cytology result (HSILor worse), the women will be offered colposcopy directed biopsies and treatment according to the cervical cancer screening national guidelines. Informed written consent will be obtained from research participants and confidentiality guaranteed.The trial will be registered at ClinicalTrials.gov and trial analyses and reports will be made in accordance with CONSORT requirements. It is an important part of the study that all women will have a cytology examination when they exit the study after 26 months and we will make sure that all women are cared for in the best possible way.

4. Expected outputs and outcomes

The project will produce 4 PhD theses, at least 14 scientific papers published in international, peer-reviewed journals, at least 5 articles published in popular journals/magazines, at least 6 conference papers (4 national and 2 international), and a minimum of 12 research updates and policy briefs.

The expected outcomes of the project are:

- New knowledge about the natural history of HPV infection and consequences of HPV infection among HIV positive and HIV negative women
- New approaches in performing cervical cancer screening. On the basis of the research, possibleimprovements of the screening program will be identified, with a particular viewto implementation of HPV testing and improved continuity of care.
- A cadre of health staff and community health workers who are trained in cervical cancer control and prevention and who through an improved communication line will help facilitate on-going care and treatment to women who are screened positive
- Improved capacities among researchers to conduct interdisciplinary and internationally informed research on primary and secondary prevention of cervical cancer
- Decreased mortality from cervical cancer due to detection of precancerous lesions and earlier detection of cervical cancer
- Reduced poverty through enhancement of women's sexual and reproductive health. To a high degree cervical cancer is diagnosed in women at reproductive age and is thus leading to high numbers of premature deaths with substantial social and economic consequences at an individual level and in society. Prevention of cervical cancer will therefore have an impact on reduction of poverty and sustainable development in society.

5. Relevance

In Tanzania, cervical cancer is the commonest type of cancer in women, and that with the highest mortality rate. Annually, approximately 7300 new cases are diagnosed and about 4200women die from cervical cancer(11). Thus cervical cancer is a public health problem that has enormous social and economic population impact as it often affects women at reproductive

age(12). To address this public health problem, the project will provide new and important information on the natural history of HPV and how it relates to HIV, information that will be of help in the development of more efficient vaccines and screening strategies that targets HIV positive and HIV negative women. The project also aims to evaluate *Care*HPV testing (a simple to do test) as a tool for cervical cancer screening and to examine how continuity of care of women who are screened positive can be improved by two simple low cost interventions. The information generated from the project will help inform the future screening strategy in Tanzania as well as in other countries with high HIV prevalence. We will make it a priority that beside the publication of our results in scientific journals, we will communicate the results to decision makers, stakeholders and to the general population.The focus areas of our research, HPV, HIV and cervical cancer are well in line with the "Tanzanian National Health Research Policy" from 2013 that lists Communicable diseases, Non-communicable diseases and Reproductive health as top-three priority areas. Our research areas are also aligned with the Tanzanian Health Sector Strategic Plan III (HSSP III 2009-2015), supported by Danida, which also lists reproductive health and communicable and non-communicable diseases as priority areas. The project does also have relevance in relation to overall objectives and priorities of Danish development cooperation as expressed in The Right to a Better Life which states that "Denmark will be at the forefront of international efforts to promote sexual and reproductive health and rights, and in the fight against HIV/AIDS". Finally, through the linkage with KCMC, the activities are also in line with Danida priorities for research capacity building, since KCMC is one of the core institutions in the Building Stronger University (BSU) program.

6. Project plan

Since the project plan is complex and dynamic with interactions between multiple WPs, the key priorities will be to facilitate the necessary interactions between the WPs and to maintain the overall scientific direction over the life of the project. The project will start in January 2015 and end in December 2019. The existing ORCI and KCMC institutional bank accounts will be used for the project; and the existing financial and procurement regulations will be used for implementing the project in Tanzania. The main project milestones and timetable are shown on **Fig. 3**. The detailed budget is attached in the main application and it shows how the resource allocation in the project will be distributed between the institutions involved over the project period.

7. Participants, organization and management

Julius Mwaiselage is a medical doctor and epidemiologist and public health specialist. He is the Director of Cancer Prevention Services at ORCI. He has 9 years experiences in cancer epidemiological research in Tanzania and has been involved in various collaborative research projects focusing on HPV prevalence, cervical cancer screening and HPV vaccine introduction in Tanzania. He has authored more than 20 scientific papers in peer-reviewed journals and supervised 3 PhD students and more than 15 master's students. **Vibeke Rasch** is a gynaecologist and professor in global reproductive health. She has almost20 years experiences in reproductive health research in Tanzania, has acted as principal responsible party in an enhancing research capacity building project in Vietnam and has been member of the BSU steering committee. She has authored more than 100 scientific publications and supervised 16 PhD students, more than half from sub-Saharan Africa and Asia. **Susanne Krüger Kjær** is a medical doctor and professor of cancer epidemiology. Her main research areas are HPV and cancer and the importance of gene-environment interactions in cancer development with a focus on clinical utility and the translational aspect. She has authored more than 350 scientific papers, and she is the Danish primary investigator on the clinical, randomised trials of the efficacy of HPV vaccination. She has supervised more than 25 Phd students. **TwalibNgoma** is a professor of oncology. He has more than 25 years of experience in teaching, clinical work and research related to cancer. He is the executive director of ORCI and the head of clinical oncology department of Muhimbili University College of Health and Allied Science. **RachelManongi** is Head of Community Medicine Department at KCMC, she has a record of community based research with a special focus on HIV prevention and sustainable health promotion and has also been active in the establishment of a cervical cancer registry at KCMC. She has authored more than 40 papers in international journals.

The project builds on and extends existing collaboration between these Tanzanian and Danish researchers. The involved Danish researchers have solid experience in research capacity building in Tanzania and in HPV research and both have strong publication records. The proposed project will be undertaken in close coordination with the research capacity building activities conducted within the BSU initiative. The overall responsibility for the project lies with the main Tanzanian applicant. To facilitate cross-country project management, a Steering Board will be established between Tanzanian and Danish collaborators. A project management unit(PMU) will be established at ORCI. The PMU will consist of a project secretary and an accountant and will be responsible for day-to-day activities. To monitor the activities, a web-based project management tool will be established. The web tool will include detailed updated work plans linked to the work packages so partners can track project progress. Project documents will be available on the web-site. Members of the Steering Board will meet on a regular basis to ensure a continuous progress of the study. In addition, annual workshop meetings will beheld with representatives from the partner institutions.

8. Project's international dimension

There is a great international interest in cervical cancer prevention focusing on different screening modalities, HPV testing and HPV vaccination, and it is one of the areas where substantial progress has been made in recent years and it is also one of the areas where research has the greatest translational potential. The suggested project relies heavily on collaboration between researchers in Tanzania, Denmark, Germany and France who have strong expertise in HPV epidemiology, HPV testing technology, cervical cancer screening approaches, and international health. Through this international collaboration, we will obtain a strong and valuable synergy. By means of this project there will be a great opportunity for transfer of knowledge and technology to Tanzania, which in a longer perspective may be further transferred to neighbouring sub-Saharan African countries with similar high prevalence rates of HPV and HIV.

9. New knowledge

Virtually all cases of cervical cancers and high-grade precursor lesions are caused by a persistent infection with HPV(13). Although effective prophylactic vaccines against HPV have been developed, they are still relatively expensive and logistically demanding as they currently require a 3-dose regimen. Furthermore, they do not treat already existing HPV infections and related diseases. Several African cross-sectional studies of the prevalence of HPV have been performed, including our own from Tanzania where we found an HPV prevalence of 20.1% among 3700 women(2). In the same study we found that 9.3% of the women were HIV positive. In contrast, only few prospective studies on HPV epidemiology have been conducted in Africa. Of these, some had a limited sample size (14), some did only include HIV negative women(9) or exclusively used self-sampled cervical swabs(15). In spite of the fact that cervical cancer is the most common malignancy among women in Sub-Saharan Africa(1), little is known about the distribution of HPV types, independent risk factors of incidence and patterns of persistence for different HPV types. Even though HPV16 has been found to be common in sub-Saharan African women, some studies have reported HPV52 and HPV58 to be more prevalent(2). Data on which HPV types are more likely to persist in relation to HIV status are scarce, particularly in HIV positive individuals. Results from the proposed study will add important information to our knowledge about the natural history of HPV in an HIV high-risk area and will be helpful in tailoring screening programs to match the needs of HIV positive and HIV negative women.

The conventional cytology screening (Pap smear followed by colposcopically-directed biopsies) demands costly cytology laboratories with skilled and highly experienced personnel, and multiple visits at regular intervals are needed. Consequently, the Pap smear screening is neither sufficiently developed nor sustainable in less developed countries(16). Therefore, cost effective methods such as VIA have been adopted in several countries for early detection of precancerous lesions. In 2002 cervical cancer screening based on VIA was implemented at

ORCI and the program has subsequently been scaled up to cover other regions in Tanzania. However, several studies, including our own recent study, have found VIA to have a limited sensitivity(4). In contrast, HPV screening is appealing due to a higher sensitivity and a higher negative predictive value(17). However, successful HPV screening in countries with limited resources requires a simple HPV test that will perform well also in remote areas and which is affordable. Finally, self-sampling will most likely be needed to make screening practical in some settings. . In relation to these issues, our study will contribute new knowledge which can immediately be used and implemented to the benefit of the women.

A successful programme for cervical cancer prevention requires function in its entirety. The programme should ensure high levels of screening coverage of the target population, offer high quality services, have good referral systems that guarantee patient follow-up and make certain that women receive appropriate treatment. Experiences from Tanzania mainland have documented that these preconditions are often not adhered to due to a poor functioning health system and as a consequence the screening results are often not conveyed and proper action not always taken. Currently, there is no mechanism in place in Tanzania to help women navigate between the potential barriers, which may be hindering factors for obtaining confirmatory diagnosis and adequatetreatment of cervical precancerous lesions. Mobile Health, which implies the use of mobile communication devices for health care, is seen as a complementary strategy for strengthening health systems and the use of SMS has successfully been used to remind patients to take drugs and attend appointment e.g.in Kenya(18). Similarly, members of our research team have documented the effect of SMS on antenatal care attendance and skilled delivery attendance in Tanzania(7).The Patient Navigation Model is an alternative approach to enhance continuity of care among underserved populations. The navigators can be trained community health workers or peer educators who provide support and guidance (19). Patient navigation is used as a standard of care in most of Western oncological departments and has been proven to be successful in several studies e.g: Cancer control among urban African American (20) and Breast cancer screening(21). Understanding the acceptance of these two proposed models among Tanzanian women detected to have HPV will help health care professionals to develop more effective continuum of care programs by promoting attendance to HPV screening and follow-up of disease progression.

10. Publication and dissemination strategy

The research findings will be communicated via a project website, scientific paper in peer-reviewed journals and popular articles. Further to get maximum impact of the findings, a stakeholder workshop focusing on cervical cancer screening and continuity of care will be held at the beginning and at the end of the project. The invitees will include Women's groups representatives, civil society, health care providers, health sector officials and researchers. The workshop will involve stakeholders in the formulation of intervention strategies, which will enhance continuity of care among women who are screened positive. Further, at the end of the project period a policy brief workshop facilitated by a communication expert will be held and will result in the formulation of a policy brief that summarizes the research findings and provides recommendations to decision makers. The policy brief will be produced and shared at a national dissemination seminar where health policy makers, Danida representatives and other relevant stakeholder are invited.

11. Strategy for phasing out of the project

The project will be undertaken in cooperation with Ministry of Health officials and with health system representatives. Based on the research conducted within each work package, concrete recommendations for improved cervical cancer prevention will be developed and shared with health policy makers and other stakeholders. Since the PI is Director of Cancer Preventive service in Tanzania at ORCI and a member of the Ministry of Health technical working group for cervical cancer prevention and control in Tanzania, he will ensure the recommendations of the project are sent to the respective authorities and implemented. Initially most of the technical recommendations from the project will be implemented at ORCI, KCMC and among cervical cancer screening implementing partners in Tanzania after update of the cervical cancer

screening national service delivery guidelines. Furthermore, through a phased and participatory approach, the policy recommendations for the Ministry of Health, will be discussed at the relevant level of authority in order to ensure the updated policy guidelines and ministerial circulars for cervical cancer include the project recommendations on improvement, particularly on continuity of care. The Tanzanian post-doctoral and PhD students will be in the forefront in the implementation and sustainability of the comprehensive cervical cancer prevention in Tanzania given the knowledge and skills obtained in the project; and it is anticipated that they will be employed by ORCI and KCMC or even at the Ministry of Health. The established cohort of HPV positive women will be kept and maintained at ORCI for future studies on HPV persistence and clearance patterns and women's absolute risk of subsequently developing precancerous lesions (17).

Fig. 1:Natural history of human papillomavirus (HPV) infection and cervical precancerous lesions

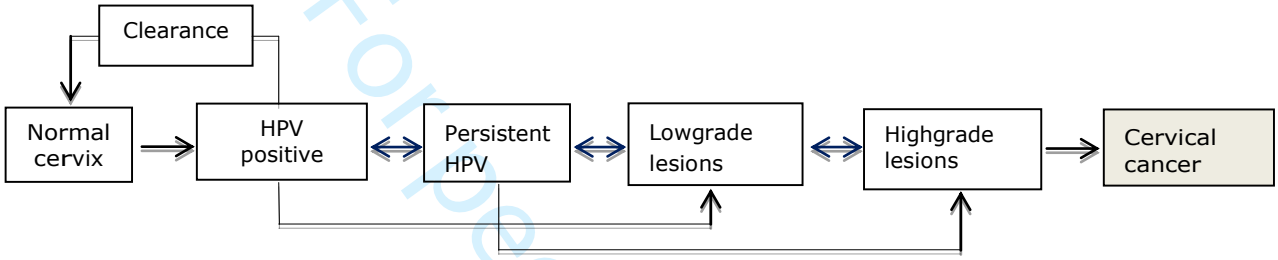
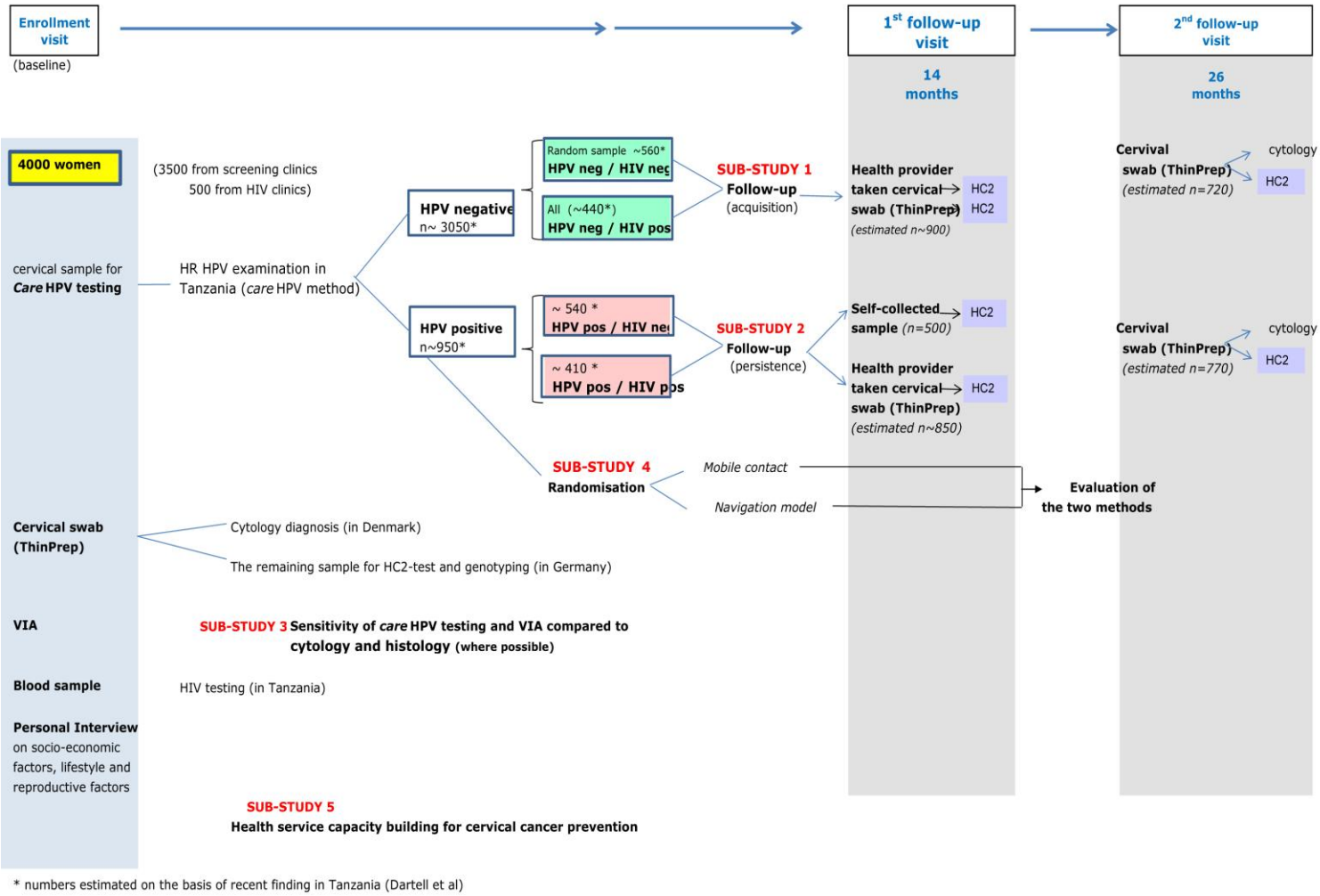


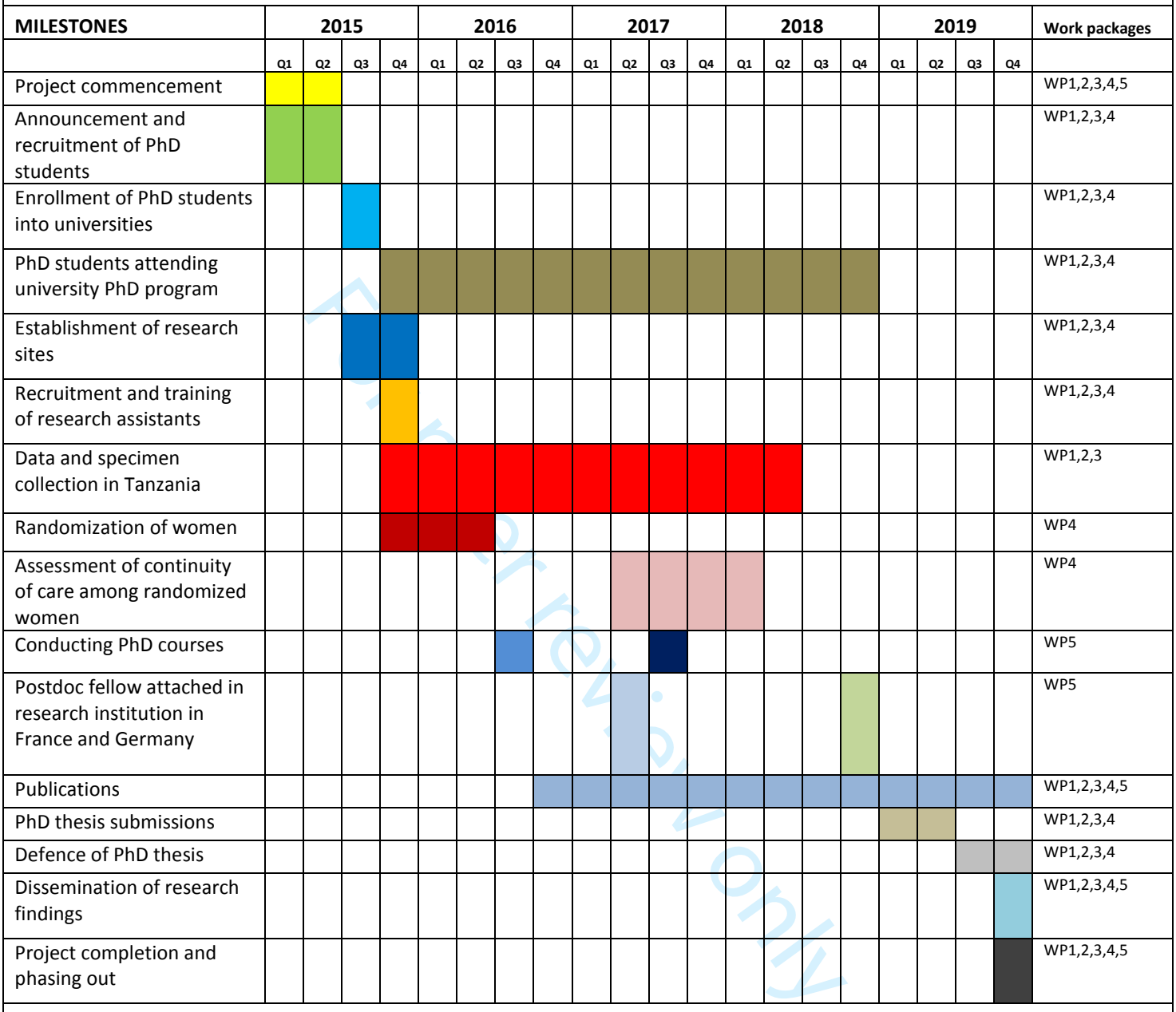
Fig 2: The schematic overview of the study design



* numbers estimated on the basis of recent finding in Tanzania (Dartell et al)

Fig 3: The schematic overview of the project milestones and timetable

FIG 3: THE SCHEMATIC OVERVIEW OF THE PROJECT MILESTONES AND TIMETABLE



Note: Project commencement involves planning meeting of researchers, setting up of the project office, and ensuring ethical clearance is obtained from relevant bodies

Note: Project completion involves writing of the final project report, final auditing of the project, phasing out of the project to ensure sustainability

12. Main References

1.**Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer 2010 Dec 15;127(12):2893-917.
2.**Dartell M**, Rasch V, Kahesa C, Mwaiselage J, Ngoma T, Junge J, et al. Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study. SexuallyTransmittedDiseases. 2012 Mar;39(3):201-8.
3. **Dartell M**, Rasch V, Munk C, Kahesa C, Mwaiselage J, Iftner T, et al. Risk factors for high-risk human papillomavirus detection among HIV-negative and HIV-positive women from Tanzania. SexuallyTransmittedDiseases. 2013 Sep;40(9):737-43.
4. **Dartell MA**, Rasch V, Iftner T, Kahesa C, Mwaiselage JD, Junge J, et al. Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative Tanzanian women. International Journal of Cancer 2014 Jan 4. PubMed PMID: 24391021. Epub 2014/01/07. Eng.
5. **Kahesa C**, Kjaer S, Mwaiselage J, Ngoma T, Tersbol B, Dartell M, et al. Determinants of acceptance of cervical cancer screening in Dar es Salaam, Tanzania. BMC Public Health. 2012;12:1093.
6. **Kahesa C**, Kjaer SK, Ngoma T, Mwaiselage J, Dartell M, Iftner T, et al. Risk factors for VIA positivity and determinants of screening attendances in Dar es Salaam, Tanzania. BMC Public Health. 2012;12:1055. PubMed PMID: 23216752.
7. **Lund S**, Hemed M, Nielsen BB, Said A, Said K, Makungu MH, et al. Mobile phones as a health communication tool to improve skilled attendance at delivery in Zanzibar: a cluster-randomised controlled trial. BJOG 2012 Sep;119(10):1256-64. PubMed PMID: 22805598.
8. **Nielsen A**, Iftner T, Munk C, Kjaer SK. Acquisition of high-risk human papillomavirus infection in a population-based cohort of Danish women.Sexually Transmitted Diseases 2009 Oct;36(10):609-15.
9. **Fukuchi E**, Sawaya GF, Chirenje M, Magure T, Tuveson J, Ma Y, et al. Cervical human papillomavirus incidence and persistence in a cohort of HIV-negative women in Zimbabwe. Sexually Transmitted Diseases. 2009 May;36(5):305-11. PubMed PMID: 19295468.
10. **Olesen TB**, Iftner T, Mwaiselage J, Kahesa C, Rasch V, Ngoma T, et al. Prevalence and type distribution of human papillomavirus among 1813 men in Tanzania and the relationship to HIV status. Sexually Transmitted Diseases. 2013 Jul;40(7):592-8. PubMed PMID: 23965778. Epub 2013/08/24. eng.
11. Human Papillomavirus and Related Diseases in Tanzania. Summary Report [Internet]. ICO Information Centre on HPV and Cancer.
12. **Chokunonga E**, Borok MZ, Chirenje ZM, Nyakabau AM, Parkin DM. Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991-2010. International Journal of Cancer 2013 Aug 1;133(3):721-9. PubMed PMID: 23364833. Epub 2013/02/01. eng.
13. **Kjaer SK**, van den Brule AJ, Bock JE, Poll PA, Engholm G, Sherman ME, et al. Human papillomavirus--the most significant risk determinant of cervical intraepithelial neoplasia. International Journal of Cancer 1996 Mar 1;65(5):601-6.
14.**Veldhuijzen NJ**, Vyankandondera J, van de Wijgert JH. HIV acquisition is associated with prior high-risk human papillomavirus infection among high-risk women in Rwanda. AIDS (London, England). 2010 Sep 10;24(14):2289-92. PubMed PMID: 20613457. Epub 2010/07/09. eng.
15. **Safaeian M**, Kiddugavu M, Gravitt PE, Gange SJ, Ssekasanvu J, Murokora D, et al. Determinants of incidence and clearance of high-risk human papillomavirus infections in rural Rakai, Uganda. Cancer Epidemiology, Biomarkers &Prevention 2008 Jun;17(6):1300-7.
16. **Denny L**. Cytological screening for cervical cancer prevention. Best practice & research Clinical obstetrics & gynaecology. 2012 Apr;26(2):189-96. PubMed PMID: 22071306. Epub 2011/11/11. eng.
17. **Kjaer SK**, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. Journal of the National Cancer Institute. 2010 Oct 6;102(19):1478-88. PubMed PMID: 20841605.
18. **Lester RT**, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. 2010 Nov 27;376(9755):1838-45. PubMed PMID: 21071074.
19. **Honeycutt S**, Green R, Ballard D, Hermstad A, Brueder A, Haardorfer R, et al. Evaluation of a patient navigation program to promote colorectal cancer screening in rural Georgia, USA. Cancer. 2013 Aug 15;119(16):3059-66. PubMed PMID: 23719894.
20. **Halbert CH**, Briggs V, Bowman M, Bryant B, Bryant DC, Delmoor E, et al. Acceptance of a community-based navigator program for cancer control among urban African Americans. Health education research. 2014 Feb;29(1):97-108. PubMed PMID: 24173501.
21. **Lee JH**, Fulp W, Wells KJ, Meade CD, Calcano E, Roetzheim R. Patient navigation and time to diagnostic resolution: results for a cluster randomized trial evaluating the efficacy of patient navigation among patients with breast cancer screening abnormalities, Tampa, FL. PloS one. 2013;8(9):e74542. PubMed PMID:

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Indicated as Cohort in all appropriate sections
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Indicated in the section "abstract"
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Explanation provided in the "Introduction "section
Objectives	3	State specific objectives, including any prespecified hypotheses	These has been provided in ll. "108-113"
Methods			
Study design	4	Present key elements of study design early in the paper	Indicated in the sub section "study design and study population", ll. 117-143.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Indicated in the sub sections "study design and study population", ll. 117-143; "assessment of exposure, ll. 147-195; "outcome measures; ll. 198-205; "table 1: Overview of data collected in the CONCEPT cohort"
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Indicated in the sub sections "study design and study population", ll. 117-143; "assessment of exposure, ll. 147-195; "outcome measures; ll. 198-205.
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA - No matching was done
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Indicated in the sub sections "assessment of exposure, ll. 147-195; "outcome measures; ll. 198-205
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Description of this item has been provided in table 1- Overview of data collection
Bias	9	Describe any efforts to address potential sources of bias	This has been described in section

			"What is being measured"
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	An overview of data management has been provided in the sub section "Data management, ll 208-214. Detailed description of the statistical analysis may be provided in the respective individual articles,
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	An overview of data management has been provided in the sub section "Data management, ll 208-214. Detailed description of the statistical analysis may be provided in the respective individual articles
		(*b*) Describe any methods used to examine subgroups and interactions	An overview of data management has been provided in the sub section "Data management, ll 208-214. Detailed description of the statistical analysis may be provided in the respective individual articles
		(*c*) Explain how missing data were addressed	Missing data selected variables are described in Table 1 and Table 2.
		(*d*) If applicable, explain how loss to follow-up was addressed	Indicated in the sub sections "study design and study population", ll. 117-143.
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	This information has been provided in the flow chart, figure 1.
		(b) Give reasons for non-participation at each stage	This information has been provided in the flow chart, figure 1
		(c) Consider use of a flow diagram	Flow chart has been provided, figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures	Relevant characteristics of the

		and potential confounders	participants and their distribution has been provided in Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Information on missing values has been provided for each variable in Table 2 & Table 3
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2 and 3 provide a measure of important events at a baseline and follow-up
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 provides Confidence interval of the important outcome measures at baseline and on follow up
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA. Cohort profile. However, summarized in "abstract".
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Indicated in the section "Strengths and limiations, ll. 264-273
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA. Cohort profile
Generalisability	21	Discuss the generalisability (external validity) of the study results	NA. Cohort profile. However, a the section "future plans", ll. 276-284 indicates future perspectives for the cohort.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Inidicated in the section "financial disclosure, ll. 294-296.

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Study number

ConcepT

Comprehensive Prevention of Cervical Cancer in Tanzania

Study site: ORCI ☐ **KCMC** ☐ **MAGOMENI** ☐ **MAWENZI** ☐

Date _____ **Study number** _____

Health Provider Initials _____ **Participant initials** _____

BACKGROUND

1.

How old are you?	☐☐ years

2. Are you:

Married, monogamous	1 ☐
Married, polygamous	2 ☐
Cohabiting	3 ☐
Single, with regular partner	4 ☐
Single, no regular partner	5 ☐
Divorced/ Widow	6 ☐

How long have you known your husband / cohabiter / regular partner?

☐☐ years ☐☐ months

3. With whom are you presently living?

Husband / cohabiter	1 ☐
Parents	2 ☐
Parents in law	3 ☐
Other relatives	4 ☐
Friends	5 ☐
Nobody	6 ☐

4. What is the highest level of formal education you have completed?

No formal education	1 ☐
Standard 1-4	2 ☐
Standard 5-7	3 ☐
Form 1-4	4 ☐
Form 5-6	5 ☐
University/college	6 ☐
Other _____ **Specify**	8 ☐

5. What is your religion?

Christian	1 ☐
Muslim	2 ☐
Other _____ **Specify**	3 ☐

LIFESTYLE HABITS AND HEALTH

6. Do you smoke cigarettes?

Yes, every day	☐ 1
Yes, at least once a week	☐ 2
Yes, but less than once a week	☐ 3
No, but I previously smoked	☐ 4
No, never → (go to question 11)	☐ 5

7. How old were you, when you started to smoke cigarettes regularly?

(i.e. at least once a week)

age _____ years

8. How many years have you smoked cigarettes regularly? (subtract periods of smoking cessation)

number of years: _____

9. **If you are a current smoker, how much do you smoke on an average day?**

number of cigarettes: _____

10. **If you no longer smoke cigarettes, how old were you when you stopped smoking?**

age _____ years

11. **Have you ever drunk alcohol and if yes, how old were you when you started drinking alcohol?**

Have never been drinking	12 years or younger	13-14 years	15-16 years	17-18 years	19-20 years	21 years or older
☐ 1 (Go to question 14)	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

12. **How much per week do you usually drink of the following types of alcohol?**

Beer	No. of glasses per week on average	
Local brew	No. of drinks per week on average	
Wine	No. of glasses per week on average	
Liquor	No. of drinks per week on average	

(**1 bottle of vine** = 6 glasses, **1 bottle of liquor** = 20 drinks, **1 bottle of beer** = 2 glasses)

13. **How many times per month on average do you have more than 6 drinks on the same occasion?**

Never	Less than once a month	1-3 times per month	4-8 times per month	≥ 9 times per month
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

14. **How do you regard your own health?**

Excellent	Very good	Good	Less good	Bad
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

15. How do you perceive your body size?

Much too thick	A little too thick	Good	A little too thin	Much too thin
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

REPRODUCTIVE HEALTH and SEXUAL HABITS

16. Have you ever been pregnant?

- yes	1 ☐	
- no	2 ☐	→ **Go to question 17**

If yes:

Total number of pregnancies	1 ☐☐
Total number of births	2 ☐☐

How old were you at the first pregnancy? ☐☐ years

How old were you when you gave birth to your first child? ☐☐ years

17. Did you ever have a sexual partner?

- yes	1 ☐	
- no	2 ☐	**Go to question 21**

If yes:

How old were you at first intercourse? ☐☐ years

How old was your first partner at that time? ☐☐ years

18. How many sexual partners did you have during your lifetime? ☐☐ number

19. Did you have sexual intercourse within the last 12 months?

- yes	1 ☐
- no	2 ☐

If yes:

How often have you used condoms during the last 12 months?

At every sexual intercourse	1 ☐
Frequently but not at every intercourse	2 ☐
Rarely	3 ☐
Only sexual intercourse without condoms	4 ☐

20. Is your husband / cohabiter / regular partner circumcised?

Yes	1 ☐
No	2 ☐
No husband / cohabiter / regular partner	3 ☐

21. Has a doctor or other health care provider told you that you had genital warts (condyloma)?

- yes	1 ☐
- no	2 ☐

If yes:

How old were you when you had genital warts for the first time? ☐☐ years

Have you had genital warts in the last 12 months?

- yes	1 ☐
- no	2 ☐

22. Have you ever been screened against cervical cancer?

- yes	1 ☐
- no	2 ☐

If yes:

Has a doctor or other health care provider told you that you had precancerous lesions on the cervix?

- yes	1 ☐	
- no	2 ☐	**Go to question 23**

When did you have your last diagnose of precancerous lesions?

☐☐ calendar month ☐☐☐☐ calendar year

Which treatment did you receive?

- Cryo therapy	1 ☐
- LEEP	2 ☐
- Don't know	3 ☐

23. Has a doctor or other health care provider told you that you had one of the following sexually transmitted diseases?

Chlamydia	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years
Gonorrhea	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years
Syphilis	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years

24. Have you ever been tested for HIV?

- yes	1 ☐
- no	2 ☐

If yes:

Have you ever tested positive?

- yes	1 ☐	
- no	2 ☐	**Go to question 25**

If yes:

When did you test positive? ☐☐ calendar month ☐☐☐☐ calendar year

When did you have your last CD4 count test?
(If more than 6 months ago → refer the woman for a new test)

☐☐ calendar month ☐☐☐☐ calendar year

What was the result of the CD4 count? _____number

Have you ever been started on ARV treatment?

- yes	1 ☐
- no	2 ☐

If yes:

				started when ?	
First line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year
Second line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year
Third line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year

What is your CTC card number? _____ Clinic name _____ Card number

What is your CTC file number? _____ File number

If you do not know, can we call you and get the number?

- yes	1 ☐
- no	2 ☐

TAARIFA KUHUSU SARATANI YA SHINGO YA KIZAZI
(KNOWLEDGE OF CERVICAL CANCER)

25. Sentensi zifuatazo zinahusu saratani ya shingo ya kizazi. Sema kweli au si kweli kwa kila sentensi

(Here are some statements about cervical cancer. I will ask you to answer which are true and which are false)

1. Malaria (mbu) inasababisha saratani ya shingo ya kizazi *(Malaria (mosquito) causes cervical cancer)*	Kweli ☐	Si kweli ☐
2. Kupata maumivu wakati wa kukojoa ni dalili ya saratani ya shingo ya kizazi *(Pain during urination can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
3. Saratani ya shingo ya kizazi ndiyo inayoongoza kwa magonjwa ya kanza za wanawake hapa Tanzania *(Cervical cancer is the most commen cancer disease among Tanzanian women)*	Kweli ☐	Si kweli ☐
4. Unaweza kupata saratani ya shingo ya kizazi kwa kubusiana *(You can get cervical cancer from deep kissing)*	Kweli ☐	Si kweli ☐
5. Inawezekana kujikinga na saratani ya shingo ya kizazi *(It is possible to prevent cervical cancer)*	Kweli ☐	Si kweli ☐
6. Kutokwa damu ukeni ni dalili kuu ya ugonjwa wa saratani ya shingo ya kizazi *(Vaginal bleeding is the most common sign of cervical cancer)*	Kweli ☐	Si kweli ☐
7. Jua kali linaweza kusababisha saratani ya shingo ya kizazi *(Too much sun can lead to cervical cancer)*	Kweli ☐	Si kweli ☐
8. Maambukizi ya kwenye shingo ya kizazi mara zote hubadilika kuwa saratani *(A cervical infection will always turn into cancer)*	Kweli ☐	Si kweli ☐
9. Wanawake wenye VVU wako kwenye hatari kubwa ya kupata saratani ya shingo ya kizazi *(HIV-positive women have higher risk of developing cervical cancer)*	Kweli ☐	Si kweli ☐
10. Saratani ya shingo ya kizazi mara nyingi hugundulika mapema kutokana na dalili zake (Cervical cancer is often found at an early stage due to obvious symptoms)	Kweli ☐	Si kweli ☐
11. Unaweza kupata saratani ya shingo ya kizazi kwa kujamiiana bila kinga *(You can get cervical cancer from unprotected sexual intercourse)*	Kweli ☐	Si kweli ☐
12. Kupima afya kunaweza kugundua maambukizi ya kwenye shingo ya kizazi na kuyazuia yasibalike kuwa saratani *(Screening can detect cervical infections so they do not develop into cancer)*	Kweli ☐	Si kweli ☐
13. Saratani ya shingo ya kizazi inaongoza kwa kusababisha vifo vinavyotokana na saratani kwa wanawake hapa Tanzania *(Cervical cancer is the main cause of cancer-related death among Tanzanian women)*	Kweli ☐	Si kweli ☐
14. Saratani ya shingo ya kizazi mara nyingi huwapata wanawake wakiwa kwenye miaka ya ishirini. *(Cervical cancer is most common for women in their 20's)*	Kweli ☐	Si kweli ☐
15. Kuwashwa ukeni kunaweza kuwa ni dalili ya saratani ya shingo ya kizazi *(Itchiness in the vaginal area can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
16. Kirusi kinachoitwa Human papilloma virus ndicho kisababishacho saratani ya shingo ya kizazi *(A virus called "Humanpapiloma virus" (HPV) causes cervical cancer)*	Kweli ☐	Si kweli ☐

UKUBALI WA UJUMBE MFUPI KUPITIA SIMU YA MKONONI
(ACCEPTANCE OF MOBILE MESSAGES)

UTANGULIZI *(Introduction):*
Kwenye utafiti huu wanawake watatakiwa kurudi baada ya miezi 14. Baadhi ya wanawake watatumiwa ujumbe kupitia simu ya mkononi wenye taarifa za afya na kukukumbusha siku ya kurudi kliniki. Nitakuuliza maswali machache kuhusu ujumbe wa kupitia simu ya mkononi

(In this study, all women will get a new appointment at the clinic after 14 months. However, some women will also receive health information and reminders of their appointment via sms. Here are some questions about mobile messages.)

26. Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au ya familia yako? (Chagua tabasamu sahihi kuonyesha utakavyojisikia)

(How do you feel about receiving health information and reminders of your appointment via sms on your or your family's mobile phone? Choose the one smiley that best shows how you feel)

Siipendi kabisa
I do not like it at all ☐

Siipendi
I do not like it ☐

Sio sawa
It is not okay ☐

Sawa
It is okay ☐

Naipenda
I like it ☐

Naipenda sana
I like it very much ☐

27. Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au ya familia yako? (Weka alama ya mstari wima kuonyesha utakavyojisikia).

(How do you feel about receiving health information and reminders of your appointment via sms on your or your family's mobile phone? Make one vertical mark on the line similar to how you feel)

Thanks a lot for your help

If there are any comments to add, please write them below

_____
Baseline Study number

_____
Follow-up Study number

ConcepT

Comprehensive Prevention of Cervical Cancer in Tanzania

FOLLOW-UP QUESTIONNAIRE

Study site: ORCI ☐ **KCMC** ☐ **MAWENZI** ☐

Date _____ **Follow-up Study number** _____

Baseline Study number_____

Health Provider Initials _____ **Participant initials** _____

REPRODUCTIVE HEALTH and SEXUAL HABITS

1. Have you given birth since your last screening visit?

- yes	1 ☐	
- no	2 ☐	→ **Go to question 2**

If yes:

Total number of pregnancies since last visit	1 ☐☐
Total number of births since last visit	2 ☐☐

2. Did you have a sexual partner since your last screening visit?

- yes	1 ☐	
- no	2 ☐	**Go to question 3**

If yes:

Have you had a *new* sexual partner since your last screening visit?

- yes	1 ☐
- no	2 ☐

How many sexual partners did you have since your last screening visit?

|__|__|__| number

How often have you used condoms since your last screening visit?

At every sexual intercourse	1 ☐
Frequently but not at every intercourse	2 ☐
Rarely	3 ☐
Only sexual intercourse without condoms	4 ☐

3. Is your husband / cohabiter / regular partner circumcised?

Yes	1 ☐
No	2 ☐
No husband / cohabiter / regular partner	3 ☐

Hormonal Family Planning

4. Have you ever used hormonal family planning methods?

- yes	1 ☐	
- no	2 ☐	**Go to question 5**

If yes:

What type of hormonal contraceptives have you used?

Type	No, never	Yes	If *yes*, how long have you used it overall?
Birth control pills	2 ☐	1 ☐	☐☐ years and ☐☐ months
Birth control shot (Depo-provera)	2 ☐	1 ☐	☐☐ years and ☐☐ months
Birth control implant (Implanon/ Nexoplan)	2 ☐	1 ☐	☐☐ years and ☐☐ months
Hormonal IUD (Mirena)	2 ☐	1 ☐	☐☐ years and ☐☐ months

HIV

5. Have you tested positive for HIV since your last screening visit?

- yes	1 ☐	
- no	2 ☐	**Go to question 6**

If yes:

When did you test positive? ☐☐ calendar month ☐☐☐☐ calendar year

When did you have your last CD4 count test?
(If more than 6 months ago → refer the woman for a new test)

☐☐ calendar month ☐☐☐☐ calendar year

What was the result of the CD4 count? _____number

Have you ever been started on ARV treatment?

- yes	1 ☐
- no	2 ☐

If yes:

			started when ?		
First line	1 ☐ Yes	2 ☐ No	**If yes**	☐☐ calendar month	☐☐☐☐ calendar year
Second line	1 ☐ Yes	2 ☐ No	**If yes**	☐☐ calendar month	☐☐☐☐ calendar year
Third line	1 ☐ Yes	2 ☐ No	**If yes**	☐☐ calendar month	☐☐☐☐ calendar year

What is your CTC card number? _____ Clinic name _____ Card number

What is your CTC file number? _____ File number

If you do not know, can we call you and get the number?

- yes	1 ☐
- no	2 ☐

ATTENDANCE TO FOLLOW-UP APPOINTMENT

6. Which of following tools were most important for you to remember your appointment today? *(choose one answer)*

I remembered from my appointment card and came to the clinic	1 ☐	**Go to question 8**
I had a sms-reminder and came to the clinic	2 ☐	**Go to question 8**
A nurse called me and told me to come to the clinic	3 ☐	**Go to question 7**
A nurse visited me at home and told me to come to the clinic	4 ☐	**Go to question 7**
A nurse visited and we had the appointment at my home	5 ☐	**Go to question 7**

7. What are the main reasons why you did not come to the clinic before the nurse contacted you?

I could not afford transportation on my own	Yes 1 ☐	No 2 ☐
I did not think the appointment was important	Yes 1 ☐	No 2 ☐
I had forgotten	Yes 1 ☐	No 2 ☐
I was nervous about the result of the screening	Yes 1 ☐	No 2 ☐
I was nervous about having a gynaecological examination	Yes 1 ☐	No 2 ☐
House chores prevented me from coming	Yes 1 ☐	No 2 ☐
The clinic is too far away from my home	Yes 1 ☐	No 2 ☐
Rainy season/ public holidays	Yes 1 ☐	No 2 ☐
My family does not know that I go, so I have to go secretely	Yes 1 ☐	No 2 ☐
I had my period	Yes 1 ☐	No 2 ☐
I was pregnant	Yes 1 ☐	No 2 ☐
I had moved	Yes 1 ☐	No 2 ☐
Other *(please write)* ……		

HEALTH EDUCATION BY MOBILE PHONE
(ELIMU YA AFIA QUA SIM)

8. Have you received any text messages (sms) regarding cervical cancer and your screening appointment at the clinic?

- yes 1 ☐	
- no 2 ☐	**(Questionnaire is <u>finished</u>)**

<u>If yes:</u>

How do you like the number of messages that you received?

Too many messages	1 ☐
Adequate amount of messages	2 ☐
Too few messages	3 ☐

How do you feel about of the following statements? *(If 'don't know' leave box empty)*

The information in the messages was easy to understand	Yes 1☐	No 2☐
I did *not* need help from others to read the messages	Yes 1☐	No 2☐
The information in messages made me uncomfortable	Yes 1☐	No 2☐
I know how to read text messages on my phone	Yes 1☐	No 2☐
I often send and receive text messages on my phone	Yes 1☐	No 2☐
I shared the health education that I got on my phone with friends or family	Yes 1☐	No 2☐
I would like to continue to receive health information by mobile phone	Yes 1☐	No 2☐
My husband or other family members was happy that I received health information on my mobile phone	Yes 1☐	No 2☐
I would recommend a friend or a family member to receive health education by mobile phone	Yes 1☐	No 2☐

How do you feel about receiving health information and reminders of your appointment via sms on your mobile? *(Choose the one smiley that best shows how you feel)*

Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au? (Chagua tabasamu sahihi kuonyesha utakavyojisikia)


I do not like it at all ☐


I do not like it ☐


It is not okay ☐


It is okay ☐


I like it ☐


I like it very much ☐

Here are some statements about cervical cancer. I will ask you to answer which are true and which are false? *(only for women that have received sms'!)*

Sentensi zifuatazo zinahusu saratani ya shingo ya kizazi. Sema kweli au si kweli kwa kila sentensi

1. Malaria (mbu) inasababisha saratani ya shingo ya kizazi *(Malaria (mosquito) causes cervical cancer)*	Kweli ☐	Si kweli ☐
2. Kupata maumivu wakati wa kukojoa ni dalili ya saratani ya shingo ya kizazi *(Pain during urination can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
3. Saratani ya shingo ya kizazi ndiyo inayoongoza kwa magonjwa ya kanza za wanawake hapa Tanzania *(Cervical cancer is the most commen cancer disease among Tanzanian women)*	Kweli ☐	Si kweli ☐
4. Unaweza kupata saratani ya shingo ya kizazi kwa kubusiana *(You can get cervical cancer from deep kissing)*	Kweli ☐	Si kweli ☐
5. Inawezekana kujikinga na saratani ya shingo ya kizazi *(It is possible to prevent cervical cancer)*	Kweli ☐	Si kweli ☐
6. Kutokwa damu ukeni ni dalili kuu ya ugonjwa wa saratani ya shingo ya kizazi *(Vaginal bleeding is the most common sign of cervical cancer)*	Kweli ☐	Si kweli ☐
7. Jua kali linaweza kusababisha saratani ya shingo ya kizazi *(Too much sun can lead to cervical cancer)*	Kweli ☐	Si kweli ☐
8. Maambukizi ya kwenye shingo ya kizazi mara zote hubadilika kuwa saratani *(A cervical infection will always turn into cancer)*	Kweli ☐	Si kweli ☐
9. Wanawake wenye VVU wako kwenye hatari kubwa ya kupata saratani ya shingo ya kizazi *(HIV-positive women have higher risk of developing cervical cancer)*	Kweli ☐	Si kweli ☐
10. Saratani ya shingo ya kizazi mara nyingi hugundulika mapema kutokana na dalili zake (Cervical cancer is often found at an early stage due to obvious symptoms)	Kweli ☐	Si kweli ☐
11. Unaweza kupata saratani ya shingo ya kizazi kwa kujamiiana bila kinga *(You can get cervical cancer from unprotected sexual intercourse)*	Kweli ☐	Si kweli ☐
12. Kupima afya kunaweza kugundua maambukizi ya kwenye shingo ya kizazi na kuyazuia yasibalike kuwa saratani *(Screening can detect cervical infections so they do not develop into cancer)*	Kweli ☐	Si kweli ☐
13. Saratani ya shingo ya kizazi inaongoza kwa kusababisha vifo vinavyotokana na saratani kwa wanawake hapa Tanzania *(Cervical cancer is the main cause of cancer-related death among Tanzanian women)*	Kweli ☐	Si kweli ☐
14. Saratani ya shingo ya kizazi mara nyingi huwapata wanawake wakiwa kwenye miaka ya ishirini. *(Cervical cancer is most common for women in their 20's)*	Kweli ☐	Si kweli ☐
15. Kuwashwa ukeni kunaweza kuwa ni dalili ya saratani ya shingo ya kizazi *(Itchiness in the vaginal area can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
16. Kirusi kinachoitwa Human papilloma virus ndicho kisababishacho saratani ya shingo ya kizazi *(A virus called "Humanpapiloma virus" (HPV) causes cervical cancer)*	Kweli ☐	Si kweli ☐

Thanks a lot for your help

If there are any comments to add, please write them below

BMJ Open

Cohort profile: The comprehensive cervical cancer prevention in Tanzania (CONCEPT) study

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Cohort profile: The comprehensive cervical cancer prevention in Tanzania (CONCEPT) study

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Abstract

Purpose

Cervical cancer is a major cause of death among women in Eastern Africa, and the distribution of HPV according to HIV-status is inadequately characterised in this region. In order to guide future cervical cancer preventive strategies that involve HPV-testing, the Comprehensive Cervical Cancer Project in Tanzania (CONCEPT) study was established in 2015. The CONCEPT cohort aims to investigate the natural history of HPV and determine acquisition and persistence patterns of high-risk (HR) HPV among HIV-positive and -negative women. Further, the influence of lifestyle and sexual/reproductive factors will be investigated. The main objective of this article is to describe how the CONCEPT cohort was established.

Participants

Women aged 25-60 years were enrolled from cervical cancer screening clinics in Dar-es-Salaam and Moshi, Tanzania. Data were collected at baseline, at 14 months (1st follow-up), and at 28 months (2nd follow-up). Biological samples included two cervical swabs for *care*HPV DNA-testing, cytology, Hybrid Capture 2, genotyping, and blood samples for HIV. Visual inspection with acetic acid was performed, and socio-demographic, lifestyle, and sexual/reproductive characteristics were collected through a standardised questionnaire.

Findings to date

4043 women were included in the cohort from August 2015–May 2017. At baseline, 696 (17.1%) women were HR HPV-positive and among these 31.6% were HIV-positive; 139 women (3.4%) had high grade squamous intraepithelial lesions. 3074 women (81%) attended the 1st follow-up. The majority attended after receiving a phone call reminder (35%) or from home via self-samples (41%). At 1st follow-up, 438 (14.4%) were HR HPV-positive and 30.4% of these were HIV-positive.

Future plans

A second follow-up is underway (17 December 2018–October 2020). We plan to integrate our data with a previous cross-sectional HPV study from Tanzania to increase the power of our findings. Researchers interested in collaborating are welcomed, either by extracting data or jointly requesting further investigation from the cohort.

Strengths and limitations of this study

- This is a large-scale longitudinal cervical cancer study conducted in an HIV endemic population that aims to address a major cause of disease among East-African women, which so far has not received much focus within global health research.
- Women are followed over a long duration of time and with a large amount of data being collected by use of questionnaires and lab tests.
- It was difficult to get women to return for follow-up screenings. However, carefully designed tracing plans and dedicated home-visiting staff entailed that we managed to attain an 81% participation rate at 1st follow-up.
- Detailed HIV documentation was challenging to obtain, which has limited the power in analyses involving HIV immunologic markers and treatment.

Introduction

Cervical cancer is a major cause of cancer-related mortality and morbidity globally. The highest prevalence is found among women aged 45-60 years[1], and the burden of disease is disproportionally distributed among

low- and middle-income countries (LMIC) and high-income countries (HIC) – LMICs account for 80% of cervical cancer cases worldwide. The global age-standardised incidence rate for cervical cancer is 14 per 100,000 women[2] while the incidence rate of cervical cancer is 42.7 per 100,0000 women in East Africa[3] and 54 per 100,000 women in Tanzania, specifically[4]. Major contributing factors to the high burden of disease in resource-limited settings includes low awareness of the disease and how to prevent it and unavailability of organised screening programmes. The standard screening test in resource-limited settings is visual inspection with acetic acid (VIA) as this can be performed by mid-level providers and allows for immediate treatment. However, the results of VIA is a subjective interpretation resulting in variable performances, and the utility is questionable in resource-limited settings when the number of screening rounds per women's lifetime is low[5].

HPV is the most common sexually transmitted infection worldwide, and there is a 60-70% life-time risk of acquiring an HPV infection among sexually active women[6]. Eighty to 90% of HPV infections clear spontaneously, however 10-20% become persistent and can develop into pre-cancerous lesions and cervical cancer over time. There are different factors associated with HPV persistence, the two most significant ones are the type of HPV involved and immunodeficiency, hence HIV-positive women have increased risk of acquiring HPV[7] and for the infection to become persistent[8 9]. HPV16 and 18 are the two most important types as these are associated with approximately 70% of all invasive cervical cancers worldwide[6]. Globally, the five most common types are HPV16, 18, 52, 31, and 58[10 11]. However, cross-sectional studies from Africa and systematic reviews on the global HPV burden indicate that the type-specific prevalence of HPV differs in Africa compared to other regions[2 12 13], specifically HPV 52, 58, 31, and 35 are more common in African countries compared to other parts of the world[14-16]. Tanzanian data from the HPV information centre has found the most prevalent HR HPV types among Tanzanian women with high grade squamous intraepithelial lesions (HSIL) to be HPV 16 (30.2%), HPV 52 (21.9%), and HPV 18 (16.7%) while the most prevalent HPV types among women with cervical cancer to be HPV 16 (47.7%), HPV 18 (18.2%) and HPV 45 (11.4%) [17]. Further, sexual, reproductive, and lifestyle factors influence HPV acquisition and persistence, including smoking, high parity, number of sexual partners, long-term use of oral contraceptives, and co-

infections with other sexually transmitted agents[18 19]. However to date, there are no adequately powered longitudinal HPV studies among middle-aged women in East Africa that explore the association of HIV, immunological factors, reproductive, and lifestyle factors on HR HPV acquisition and persistence.

To our knowledge, only two HPV cohort studies and one large HPV cross-sectional study have been conducted in Africa, which explore the dynamics of HPV, HIV, and cervical cancer, namely (I) the HPV in Africa Research Partnership (HARP) HPV Study in Burkina Faso and Tanzania[20]; (II) the African Collaborative Center for Microbiome and Genomics Research (ACCME) study in Nigeria[21]; and (III) the Prevention of Cervical Cancer in Tanzania (PROTECT) study[22]. Other studies are nested in HPV vaccine trials[23-25]. These studies have provided some insight into the distribution of HPV among different African populations, however, they were either cross-sectional or conducted among adolescents' with inadequately powered HIV-positive women and with a relatively short duration of follow-up.

The Comprehensive Cervical Cancer Prevention in Tanzania (CONCEPT) study was launched in 2015 with an overall aim of improving prevention of cervical cancer in Tanzania (online supplementary appendix 1). The CONCEPT study is an international collaborative study between Ocean Road Cancer Institute (ORCI), Kilimanjaro Christian Medical Centre (KCMC), University of Southern Denmark, and the Danish Cancer Society Research Center. The CONCEPT study has several specific objectives; (I) To investigate the natural history of HPV and its associated factors; (II) To determine the feasibility and acceptability of HPV self-sampling[26] and the test performance of *care*HPV compared to (HC2) and VIA[11]; and (III) how to ensure follow-up of HPV-positive women, and elucidate what motivates or prevents these women from attending to follow-up visits[27 28 29]. Introduction of HPV DNA testing in LMIC is challenging due to logistical problems inherent in these settings, however, HPV-based primary screening is a key method in future screening programmes across the world[26], and for it to be effectively established in resource-limited settings, local specific evidence is warranted. The aim of this article is to describe how this cohort was established and followed up, the profile of the cohort, and provide some characteristics of the cohort at enrolment and at the

1st follow-up. The specific objectives of the CONCEPT study have been and will be published in separate papers[11 28 30-33].

Cohort description

Study design and study population

This study was conducted in Tanzania, which is a low-income country located in Eastern African with a population of 56 million people[10]. Women were enrolled from three existing cervical cancer screening clinics located in urban and semi-rural areas; (1) ORCI in Dar-es-Salaam as well as (2) KCMC and (3) Mawenzi regional referral hospital in the Kilimanjaro region. ORCI is a national cancer hospital that provides clinical care and treatment for all the cancer patients in the country. Additionally, they conduct cervical cancer screening three times a week for the general population. KCMC is a Northern zonal tertiary facility which provides cervical screening three times a week for general population, and Mawenzi Hospital is a regional hospital which provides cervical cancer screening two times a week. In Dar-es-Salaam, women from Ilala, Temeke, and Mwananyamala district were included while in the Kilimanjaro region, women originating from the urban and rural district of Moshi – including Hai and Rombo – were included. Originally, the study was designed as a double-site study (KCMC/ORCI), however, due to a slower-than-anticipated recruitment rate, a third study site (Mawenzi) was added six months into the enrolment period. Women were eligible for inclusion if they were 25-60 years and attended a patient-initiated routine cervical cancer screening at one of the study sites. Women were excluded if they were pregnant, on their menstrual period, had a history of premalignant lesions of the cervix within the last 12 months, had previously been diagnosed with cervical cancer or had undergone abdominal hysterectomy. Women on their menstrual period were encouraged to return once their menstrual period was over. Following a detailed explanation of the study, all participants provided written informed consent. Fingerprints were used for illiterate participants. The CONCEPT study was approved by the Ethical Committee of the Tanzanian National Institute of Medical Research (NIMR/HQ/R.8a/Vol.IX/1955), and is reported according to the Strengthening the Reporting of

Observational studies in Epidemiology (STROBE) statement (online supplementary appendix 2). HIV-positive women were oversampled from Care and Treatment Clinics (CTC) at the study sites from where they were referred to the screening clinics. The total number of women and HIV-positives required for the study was found through a power calculation based on McNemar's test comparing two diagnostic tests (S1: standard test (VIA) versus S2: new test (careHPV) with cervical cytology as the reference test and the threshold being HSIL+ (HSIL, carcinoma in situ and carcinoma). The power calculation was based on the research group's previous study in Tanzania[22]. It was estimated that 180-200 women would have precancerous lesions at baseline (~true positives) and assuming a significance level of 5%, 80% power, and a sensitivity of VIA of 30%, it would be possible to detect a significant difference if the sensitivity of the new test would be at least 44%. It was anticipated that *care*HPV testing would have a higher sensitivity than VIA.

Data were collected during the enrolment visit, at 14 months (1st follow-up), and at 28 months (2nd follow-up, ongoing). As there is no a predefined optimal duration of time to investigate the natural history of HPV, the length of follow-up was based on a number of factors, including the recommended duration of time between cervical cancer screenings for HIV-positive women (12 months)[34], available resources, risk for developing cervical lesions, and limiting the workload at the screening clinics by minimising overlaps between enrolment and follow-up visits. Healthcare providers working at the screening clinics enrolled participants and collected data following protocols developed specifically for the project. At inclusion, all participants were given a 14-months follow-up appointment written on an appointment card. If the women did not attend their follow-up visit within one month of their appointment, an active follow-up procedure was initiated. Firstly, non-attendees were contacted by phone and encouraged to attend (tracing method I). If the woman did not show up within two weeks of the phone call, the women had a home-visit by an outreach nurse who encouraged her to attend (tracing method II). If the woman still did not attend and consented to it, an outreach nurse visited her again and conducted the follow-up visit at home (tracing method III). Transportation costs were compensated for those women who were reminded to come. Women, who participated in the first follow-up were appointed a second follow-up visit 28 months after initial recruitment. If the woman did not attend the 2nd follow-up, tracing method I and III were re-initiated.

Assessment of exposure

At inclusion, socio-demographic, lifestyle, reproductive, and sexual characteristics were collected during a personal interview using a modified version of a standardised questionnaire adopted from a previous study conducted in Tanzania[35] (supplementary online appendix 3). The questionnaire was hardcopy, developed in English while the interview was conducted in Kiswahili with direct translation. A Kiswahili version of the questionnaire was available to guide the interviewers. A detailed contact information form was filled at enrolment and updated at follow-up. Participants were screened by trained healthcare providers according to the standard national cervical cancer screening prevention programme in Tanzania[36]. This entails a cost-free gynaecological examination with VIA, HIV-testing and HIV-counselling. Venous blood from the index finger was tested by use of a quick HIV-1/2 test (www.alere.com), and a supplementary quick HIV-1/2 test (Abbott Laboratories) was performed as confirmatory for positive results. Discordant results were further confirmed using Unigold (Trinity Biotech). Women who screened VIA-positive or were suspected of manifest cancer were managed on-site based on the National Cervical Cancer Service Delivery Guidelines. This included treatment with cryotherapy or loop electrosurgical excision procedure (LEEP) for VIA-positives, and punch biopsy and referral for treatment at the oncology clinic at ORCI for cancer suspicions[36]. Further, weight and height were measured and registered on a hard-copy registration sheet together with the HIV- and VIA-result (Table 1).

206 **Table 1. Overview of data collected in the CONCEPT cohort**

	Measurements	Instrument	Storage and analysis
Baseline 17 Aug 2015 – 6 Jul 2017	**Biological samples** 1 provider-collected cervical swab for: • *care*HPV® DNA-testing	• Aryes spatula • Kept in *care*HPV collection medium	• Samples stored on-site in laboratories at room temperature • When 90 samples were available they were processed on-site on a *care*HPV machine • Results registered on *care*HPV sheet and stored on-site
	1 provider-collected cervical swab for: • Cytology • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula • Kept in PreServCyt solution	• Samples stored on-site in laboratories at room temperature until enrolment had finished • Then the samples were sent to the Pathology Department at Lillebaelt Hospital, Denmark and processed on the ThinPrep5000 Autoloader Instrument, Hologic® for cytology • Remaining material of the samples were sent to the Section for Experimental Virology, Tubingen University, Germany and underwent HC2 DNA testing and genotyping using LiPaExtra • Cytology and HC2 and genotype results were sent to OUH, Denmark
	Venous blood from index finger for: • HIV-test	• Quick HIV-1/2 test	• Immediate results registered on registration form and stored on-site
	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• Immediate results registered on registration form and stored on-site
	Anthropometric measures • Weight • Height	• Scale and altitude meter	• Immediate results registered on registration form and stored on-site
	Personal interview • Socio-demographic factors • HIV treatment and CD4 count • Lifestyle factors • Sexual and reproductive factors	• Structured questionnaire	• Interviewed by nurse and stored on-site • CD4 count abstracted from CTC cards and further traced in patient files
14-months follow-up (1st) 17 Oct 2016 – 6 Oct 2018	**Biological samples** 1 provider-collected cervical swab *or* self-collected swab for: • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula (provider-based) • Evalyn® brush (self-swab) • Kept in PreServCyt solution	• Self-swabs were conducted in the women's home (cf. tracing method III) and transferred to the study sites where they were stored with ThinPrep samples similarly to baseline until 1st follow-up had finished • Then the samples were sent to the Section for Experimental Virology, Tubingen University, Germany and underwent HC2 DNA testing and genotyping using LiPaExtra • HC2 and genotype results were sent to OUH, Denmark
	Venous blood from index finger for: • HIV-test (if negative at baseline)	• Quick HIV-1/2 test	• Immediate results registered on registration form and stored on-site • HIV-test was not conducted on women who participated from home (cf. tracing method III)

	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• Immediate results registered on registration form and stored on-site • Not conducted on women who participated from home (cf. tracing method III)
	Personal interview • HIV treatment and CD4 count • Sexual factors	• Structured questionnaire	• Interviewed by nurse at clinic or at home and stored on-site • CD4 count abstracted from CTC cards and further traced in patient files
28-months follow-up (2nd) (17 December 2017 – primo October 2020)	**Biological samples** 1 provider-collected cervical swab *or* self-swab only for HPV-positive women: • HC2 • Genotyping	• ThinPrep® Pap Test plastic spatula (provider-based) • Evalyn® brush (self-swab) • Kept in PreServCyt solution	• *Same procedure as in 1st follow-up*
	Venous blood from index finger for: • HIV-test (if negative at 1st follow-up)	• Quick HIV-1/2 test	• *Same procedure as in 1st follow-up*
	Visual assessment • VIA	• Acetic acid applied to cervix and abnormal tissue temporarily appears white	• *Same procedure as in 1st follow-up*
	Personal interview • HIV treatment and CD4 count • Sexual factors	• Structured questionnaire	• *Same procedure as in 1st follow-up*

Prior to the routine VIA examination, cervical swabs were taken using (I) an Aryes spatula for *care*HPV test (www.qiagen.com), and another specimen was taken using (II) a ThinPrep® Pap Test Plastic Spatula for liquid-based cytology, HPV DNA testing and genotyping by use of HC2 and LiPaExtra (Innogenetics, Gent, Belgium). The cervical samples for *care*HPV analysis were kept in a *care*HPV collection medium and stored at room temperature (max 25°C) in laboratories at ORCI or KCMC. Once 90 samples had been collected, they were analysed for HR HPV using a *care*HPV machine. A test was considered positive if one or more of the following 14 HR HPV types were detected: HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. The results were registered on a *care*HPV results sheet (Table 1).

The samples for HC2 testing, genotyping, and cytology were kept in a PreServCyt solution (Hologic, Inc. 250 Campus Drive Marlborough, MA 01752 USA) and stored at room temperature in laboratories at ORCI and KCMC. Once enrolment had finished, the PreServCyt vials were sent to the Department of Pathology at

Lillebaelt Hospital, Vejle, Denmark and processed at the ThinPrep5000 Autoloader Instrument, Hologic® according to manufactures instruction and stained with ThinPrep Stain®. The slides were scanned by the Thin Prep Imaging System® with selection of 22 Fields of view which was reviewed by cytotechnologist in review scopes. The specimens were evaluated for adequacy and for abnormal cells. If abnormal cells were detected, the slides were consulted with a gynae-pathologist who made the final diagnosis. The specimens were diagnosed according to the Bethesda Nomenclature for System for Cervical Cytology 2014[37]into following categories: Negative for intra epithelial lesion (NILM), Atypical squamous cell of undetermined significance (ASCUS), Atypical squamous cell in which High grade squamous intraepithelial lesion cannot be excluded (ASCH), Low grade squamous intraepithelial Lesion (LSIL), HSIL, Atypical glandular cell (AGC), Adenocarcinoma in situ (AIS), and Adenocarcinoma. The remaining material of the PreServCyt vials were sent to the Section for Experimental Virology, Tubingen University, Germany for HPV DNA testing and genotyping. HPV DNA testing was done using HC2 DNA test (www.qiagen.com) with a HR cocktail probe. A test was considered positive if one or more of the following 14 HR HPV types were found: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68. A threshold of 1.0pg HPVDNA/ml, which corresponds to 1.0 relative light unit coefficient, was used, as recommended by United States Food and Drug Authority. HPV-positive samples were genotyped using LiPaExtra, which can detect 28 HPV types, 18 HR risk types (HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82) and 10 low risk types (HPV 6, 11, 40, 43, 44, 54, 69, 70, 71, 74)[38].

Outcome measures

Women who attended their follow-up appointment at the screening clinics were HIV-tested (if negative at baseline), had a cervical swab collected with a ThinPrep® Pap Test Plastic Spatula – for HPV DNA testing by use of HC2 and genotyping by use of LiPaExtra – and underwent VIA (Table 1). Further, sexual and reproductive characteristics were updated by use of a structured questionnaire (online supplementary appendix 4). Women who did not attend their follow-up appointment at the clinic but consented to having a home-visit appointment (cf. tracing method III) responded to the questionnaire and had cervical specimens

collected by use of an Evalyn self-sampling/self-swab device (www.roversmedicaldevices.com). The samples were transferred to laboratories at ORCI and KCMC where they were kept in a PreServCyt solution and stored at room temperature.

Data management

Questionnaires, registrations forms, contact forms, and *care*HPV result sheets were stored in different cabinets in locked offices at KCMC and ORCI, after which they were double entered into EpiData by data clerks. Together with lab results these data were sent to the Research Unit for Gynaecology& Obstetrics, Odense University Hospital (OUH), Odense, Denmark where they were merged and constructed into a baseline database. Data with invalid IDs or no data registered were excluded upon creation of the database. Similarly to baseline, follow-up data were sent to OUH after which it was merged with the baseline database. Follow-up IDs that could not match a baseline ID were excluded.

Patient and public involvement

Study participants were not involved in the design or recruitment of the study. In order to provide increase public awareness, government and religious leaders were informed about the project, the latter through mosques and churches. When the study finishes, the results and their potential implication to the public will be communicated through meetings with health authorities, policy briefings, and announcements in the mainstream media.

Findings to date

Baseline findings

A total of 4080 women were enrolled into the CONCEPT study. After inclusion, 37 study participants were excluded leaving the total cohort to consist of 4043 women (fig 1). The baseline distribution of the socio-demographic is presented in Table 2. A total of 718 women (17.8%) were HIV-positive and the majority of

these were 35-39 years old (22.9%) while the majority of HIV-negative women were 40-44 years old (19.2%). Among the HIV-positives, 49.7% were married (n=356) whilst 73.6% of HIV-negatives were married (n=2434). Most of both HIV-positive (70.4%; n=504) and HIV-negative women (64.1%;n=2127) had completed primary school. More HIV-negative women (87.0%; n=2879) reported to have had sex within the last 12 months compared to HIV-positive women (72.7%; n=520), while more HIV-positives (26.2%) than HIV-negatives (9.8%) reported to have had used condoms at every intercourse. In relation to number of lifetime partners, 71.9% of HIV-positives reported having more than one lifetime partner whilst the corresponding number for HIV-negative women was 61.0%. The CD4 count for HIV-positive women were as follows: 8.6% (n=62) reported having a CD4 count ≤199; 30.5% (n=219) had a CD4 ranging from 200-499; and 48.9% (n=347) had a CD4 count ≥500. Further, 12.5% (n=90) of the HIV-positives did not report the CD4 count.

Table 2: Selected socio-demographic, lifestyle, sexual and reproductive characteristics of the cohort at baseline and 1st follow-up stratified according to HIV-status

	COHORT PROFILE AT BASELINE						COHORT PROFILE AT 1ST FOLLOW-UP					
	Total (n=4043)		HIV-positive (n=718; 17.8%)		HIV-negative (n=3325, 82%)		Total (n=3074)		HIV-positive* (n=552; 18.0%)		HIV-negative* (n=2522; 82.0%)	
	N	%	N	%	N	%	N	%	N	%	N	%
Age												
25-29	527	13.0	43	6.0	484	14.6	344	11.2	26	4.7	318	12.6
30-34	599	14.8	78	10.9	521	15.7	432	14.1	61	11.1	371	14.7
35-39	744	18.4	164	22.9	580	17.5	547	17.8	121	21.9	426	16.9
40-44	787	19.5	149	20.8	638	19.2	634	20.6	115	20.8	519	20.6
45-49	667	16.5	138	19.2	529	15.9	522	17.0	112	20.3	410	16.7
50-60	716	17.7	145	20.2	571	17.2	595	19.4	117	21.2	478	18.9
Missing	3	0.1	1	0.14	2	0.06	-	-	-	-	-	-
Marital status												
Married	2790	69.0	356	49.7	2434	73.6	2159	70.2	288	52.2	1871	74.2
Cohabiting	58	1.4	14	2.0	44	1.3	44	1.4	11	2.0	33	1.3
Single	487	12.0	110	15.4	377	11.4	335	10.9	76	13.8	259	10.3
Divorced/widow	687	17.0	236	33.0	451	13.6	527	17.1	176	31.9	351	13.9
Missing	21	0.5	2	0.28	19	0.57	9	0.3	1	0.2	8	0.3
BMI												
Underweight	96	2.4	27	3.9	69	2.1	73	2.4	21	3.8	52	2.1
Normal	1149	28.4	269	38.5	880	27.3	839	27.3	199	36.1	640	25.4
Overweight	2190	54.2	334	47.8	1856	57.6	1695	55.1	259	46.9	1436	56.9
Obese	486	12.0	69	9.9	417	12.9	406	13.2	59	10.7	347	13.8
Missing	122	3.0	19	2.15	103	3.1	61	2.0	14	2.5	47	1.9
Education level												
No formal education	126	3.1	32	4.5	94	2.8	89	2.9	23	4.2	66	2.6
Primary	2631	65.1	504	70.4	2127	64.1	2027	65.9	381	69.0	2027	65.3

Secondary	882	21.8		146	20.4		736	22.2		672	21.9		123	22.3		672	21.8
College	396	9.8		34	4.7		362	10.9		280	9.1		23	4.2		280	10.2
Missing	8	0.2		2	0.28		6	0.18		6	0.2		2	0.4		6	0.7
Religion																	
Christian	2708	67.0		505	70.6		2203	66.8		2064	67.1		391	70.8		1673	66.3
Muslim	1289	31.9		206	28.8		1083	32.8		978	31.8		155	28.1		823	32.6
Other	16	0.4		4	0.6		12	0.4		13	0.4		4	0.7		9	0.4
Missing	30	0.7		3	0.42		27	0.81		19	0.6		2	0.7		17	0.6
No of living children																	
0	35	0.9		5	0.7		30	0.9		22	0.7		4	0.7		18	0.7
1-2	1506	37.2		295	41.8		1211	37.5		1112	36.2		219	39.7		893	35.4
3	901	22.3		180	25.5		721	22.3		729	23.7		141	25.5		588	23.2
4-6	1135	28.1		183	25.9		952	29.5		900	29.3		150	27.2		750	29.7
>7	139	3.4		19	2.7		120	3.7		99	3.2		12	2.2		87	3.5
Never been pregnant	221	5.5		24	3.4		197	6.1		144	4.7		16	2.9		128	5.1
Missing	106	2.6		12	1.67		94	2.83		68	2.2		10	1.8		58	2.3
Years living with partner																	
0-1	166	4.1		21	3.0		145	4.4		102	3.3		18	3.3		84	3.3
2-4	517	12.8		112	15.9		405	12.4		355	11.6		74	13.4		281	11.4
5-9	723	17.9		143	20.3		580	17.8		515	16.8		106	19.2		409	16.2
10-14	648	16.0		125	17.7		523	16.0		502	16.3		97	17.6		405	16.1
15-19	546	13.5		104	14.8		442	13.6		443	14.4		85	15.4		358	14.2
>20	1203	29.8		162	23.0		1041	31.9		993	32.2		137	24.8		856	33.9
Single with no regular partner	163	4.0		38	5.4		125	3.8		118	3.8		27	4.9		91	3.6
Missing	77	1.9		13	1.81		64	1.92		46	1.5		8	1.5		38	1.5
Sex in last 1 year																	
Yes	3399	84.1		520	72.7		2879	87.0		2583	84.0		404	73.2		2179	86.4
No	610	15.1		195	27.3		415	12.5		478	15.6		146	26.5		332	13.2
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	20	0.5		3	0.42		17	0.51		8	0.3		2	0.4		6	0.2
Condom use within last 12 months																	
No sex within last 12 months	610	15.1		195	27.3		415	12.6		478	15.6		146	26.5		332	13.2
At every intercourse	509	12.6		187	26.2		322	9.8		381	12.4		139	25.2		242	9.6
Rarely	204	5.0		29	4.1		175	5.3		146	4.8		25	4.5		121	4.8
No condom use	2678	66.2		303	42.4		2375	71.9		2052	66.8		239	43,3		1813	71.9
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	28	0.7		4	0.56		24	0.72		12	0.4		3	0.5		9	0.4
Number of lifetime partners																	
1	1476	36.5		197	28.1		1279	39.0		1129	36.7		158	28.6		971	38.5
2	1053	26.0		194	27.7		859	26.2		819	26.6		155	28.1		664	26.3
3	709	17.5		147	21.0		562	17.1		516	16.8		101	18.2		415	16.5
4	284	7.0		60	8.6		224	6.8		221	7.2		46	8.3		175	6.8
5-8	329	8.1		65	9.3		264	8.1		255	8.3		49	8.9		206	8.2
>9	113	2.8		38	5.4		75	2.3		89	2.9		33	6.0		56	2.2
Never had sex	14	0.3		0	-		14	0.4		5	0.2		0	0.0		5	0.2
Missing	65	1.6		17	2.4		48	1.4		40	1.3		10	1.8		30	1.2

**According to HIV-status at baseline*

Among the 4043 participants, the cervical sample was insufficient for HPV analysis for 396 women (9.8%) at baseline, leaving 3667 women eligible for analysis of HPV-positivity. Further, 27 women (0.5%) did not

have a sample for cervical cytology, leaving 4016 women available for cytological analysis of cervical lesions. All 4043 women were either tested for HIV or had previously tested HIV-positive. At baseline, 696/4043 women (17.2%) tested HR HPV-positive by HC2. The cytology showed that overall 3.4% (n=139/4043) had HSIL+ whilst 8.1% (n=329/4043) of women had LSIL. A total 3416 women had both HPV- and cytology results. Among this subgroup of women, 18.9% were HPV-positive (n=644/3416), and the four most common HR HPV types were HPV 52 (3.8%), HPV 16 (3.6%), HPV 58 (2.5%) and HPV 18 (2.4%). Among HIV-positive women, 33.7% were HR HPV positive while the corresponding figure among HIV-negative women was 15.6%. Among women with high grade lesions (HSIL+), 32.5% had HPV 16, 19.3% had HPV 58, 17.5% had HPV 31, 16.7% had HPV 18, and 16.7% had HPV 52. A full description of the HPV distributions according to HIV status and cytology results are published elsewhere[33].

1st follow-up findings

A total of 3805 women (94%) were eligible for 1st follow-up – 238 women (6%) were ineligible due to becoming pregnant, having moved, having had a hysterectomy or having become sick or died (fig 1). Of the 3805 women, 3074 women (81%) attended the first follow-up visit approximately 14th months after enrolment. However, among the attendees only 500 (16%) attended within in 30 days of their scheduled appointment date and without being traced for follow-up. A total of 1088 (35%) attended the clinic after a phone call reminder (tracing method I), 62 women (2%) attended the clinic after a nurse home-visit (tracing method II), whilst 1253 women (41%) were followed up at home and had specimens collected using self-sampling device (tracing method III). A total of 731 women (19%) were lost to follow-up (fig 1).

(Fig 1: Flow chart of enrolment and follow-up of CONCEPT cohort)

The women who participated in the 1st follow-up were very similar to those who did not attend when looking at socio-demographic factors (table 2). However, overall fewer women were HR HPV-positive at follow-up

compared to baseline (14.8% vs. 17.2%), and fewer HIV-positive women were HR HPV-positive at follow-up compared to baseline (24.1% vs. 31.6%) (table 3).

Table 3. HR HPV, HIV, and cytology results at baseline and 1st follow-up

	Baseline				First follow up		
	Total(N=4043)				Total(N=3074)		
HPV	**n**	**%**	**(95% CI)**		**n**	**%**	**(95% CI)**
Positive	696	17.2	(0.16-0.18)		438	14.3	(0.13-0.16)
Negative	2951	73	(0.72-0.74)		2595	84.4	(0.83-0.86)
Missing	396	9.8	(0.09-0.1)		41	1.3	(0.01-0.02)
HIV							
Positive	718	17.8	(0.17-0.19)		552	18	(0.17-0.2)
Negative	3325	82.2	(0.81-0.83)		2522	82	(0.80-0.83)
Cytology							
HSIL	139	3.4	(0.03-0.04)				
LSIL	329	8.1	(0.07-0.09)				
Negative	3548	87.8	(0.87-0.89)				
Missing	27	0.7	(0.00-0.01)				

Strengths and Limitations

This is a large-scale longitudinal cervical cancer study conducted in an HIV endemic population that aims to address a major cause of disease among East-African women, which so far has not received much focus within global health research. Women are followed over a long duration of time and with a large amount of data being collected by use of questionnaires and lab tests. Given the nature of our study a significant attrition rate was expected. However, with the carefully designed tracing plans and dedicated home-visiting staff we managed to attain an 81% participation rate at 1st follow-up. As women were enrolled during a patient-initiated screening at screening clinics, detailed HIV documentation was challenging to obtain as CTC cards were poorly documented or had not been brought to the screening. Despite the nurses calling

these women after enrolment to retrieve the information, it was not provided by many HIV-positive participants. This has led to a certain amount of missing values for a few variables and have limited our ability and power in analyses involving HIV immunologic markers and treatment. The HPV distribution found in this study population in comparison to data from the source populations shows that the distribution is somewhat comparable though it also differs to a high extent on some accounts. We found that among women with HSIL+, our study population had a higher prevalence of HPV 16 (32.5% versus 30.2%) and HPV 58 (19.3% versus 6.3%), a lower prevalence of HPV 52 (16.7% versus 21.9%) while the prevalence of HPV 18 was the same (16.7%)[17]. However, the data on the source population is based on one study conducted on ORCI in Dar es Salaam in 2014[10], hence, the difference in the HPV distribution does not necessarily suggest that our study population is not generalisable to the source population but rather that it builds a stronger basis for understanding the true HPV distribution in Tanzania.

Future plans

A second follow-up is underway (17 December 2018 – primo October 2020). Based on our large-scale data of both HPV infection in general and type specific characterised by the women's HIV-status, we plan to integrate this data with a previous cross-sectional HPV study (PROTECT Study) conducted in this population as this can increase power in our findings. As we have already established a large cohort of participants, we foresee a potential to further characterise the HPV burden and establish risk factors over a longer course of time. Specifically, we wish to compare the clinical performance of three potential cervical cancer screening strategies in Tanzania, namely (I) HC2 testing at varying cut-points of viral load as measured by the RLU value; (II) HC2 testing with VIA triage; and (III) HC2 testing with triage using HPV16/18 genotyping. Further, we also foresee the possibility of linking our evidence with other groups in this population including males, adolescents, and pregnant women. This may provide additional information on the similarities of epidemiological burden among these group and delineate differences in the correlations of HPV and HPV-related disease across these different groups.

Collaboration

Researchers interested in collaboration in this discipline especially in East and Central Africa are welcomed. This may be in extracting data from the project, jointly requesting further investigation from the cohort.

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Contributors

JM, RM, VR, and SKK designed the CONCEPT study. JM, RM, VR, SKK, JK, PS, CK, BM, and DSL were involved in collecting data for the study. CW, SKK, VR, BM, and DSL, were involved in data analysis and interpretation. CW, BM, DSL contributed to the conception of this article, and CW, BM, DSL, PS, JK, CK, VR, JM, SKK, and RM were involved in the manuscript writing and revision. All authors read and approved the final manuscript.

Data sharing statement

Data collected for the CONCEPT cohort study are available upon request. Individual participant data will de-identified. Additional available data include the CONCEPT eligibility and informed consent form, the CONCEPT contact information form, the protocol for how to deliver HPV-positive results to participants, the protocol for how to trace non-attendants. Data will be made available upon request by contacting the first or last author of this study by email at barikimchome@gmail.com/dsondergaard@health.sdu.dk, who will then seek approval by the primary investigator in the CONCEPT project, Julius D. Mwaiselage.

Competing interests

There are no competing interests for any author.

Supplementary material

Supplementary appendix 1	Original protocol for CONCEPT study
Supplementary appendix 2	STROBE checklist
Supplementary appendix 3	CONCEPT baseline questionnaire
Supplementary appendix 4	CONCEPT 1st follow-up questionnaire

Abbreviations

ACCME	African Collaborative Center for Microbiome and Genomics Research
AGC	Atypical glandular cell
AIS	Adenocarcinoma in situ
ASCUS	Atypical squamous cell of undetermined significance
ASCH	Atypical squamous cell in which High grade squamous intraepithelial lesion cannot be excluded

CTC	Care and treatment clinic
CONCEPT	Comprehensive Cervical Cancer Prevention in Tanzania
Danida	Danish International Development Agency
HARP	HPV in Africa Research Partnership
HC2	Hybrid Capture 2
HIC	High-income countries
HIV	Human immuno-deficiency virus
HPV	Human papilloma virus
HSIL	High grade squamous intraepithelial lesion
KCMC	Kilimanjaro Christian Medical Centre
LEEP	Loop electrosurgical procedure
LMIC	Low- and middle-income countries
LSIL	Low grade squamous intraepithelial lesion
NILM	Negative for intra epithelial lesion
PROTECT	Prevention of Cervical Cancer in Tanzania
ORCI	Ocean Road Cancer Institute

Figure legends

Figure 1 Flow chart of enrolment and follow-up of CONCEPT cohort

References

1. Organization WH. Improving data for decision-making: a toolkit for cervical cancer prevention and control programmes. 2018. http://apps.who.int/iris.
2. Serrano B, Brotons M, Bosch FX, et al. Epidemiology and burden of HPV-related disease. *Best Pract Res Clin Obstet Gynaecol* 2018;47:14-26. doi: 10.1016/j.bpobgyn.2017.08.006 [published Online First: 2017/10/19]

3. Torre LA, Islami F, Siegel RL, et al. Global Cancer in Women: Burden and Trends. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2017;26(4):444-57. doi: 10.1158/1055-9965.epi-16-0858 [published Online First: 2017/02/23]
4. Bruni LB-RL AG, Serrano B. Human Papillomavirus and Related Diseases in Tanzania.Summary Report. *ICO Information Centre on HPV and Cancer (HPV Information Centre)* 2016;15
5. Fokom-Domgue J, Combescure C, Fokom-Defo V, et al. Performance of alternative strategies for primary cervical cancer screening in sub-Saharan Africa: systematic review and meta-analysis of diagnostic test accuracy studies. *BMJ (Clinical research ed)* 2015;351:h3084. doi: 10.1136/bmj.h3084 [published Online First: 2015/07/05]
6. Bruni L, Diaz M, Castellsague X, et al. Cervical human papillomavirus prevalence in 5 continents: meta-analysis of 1 million women with normal cytological findings. *The Journal of infectious diseases* 2010;202(12):1789-99. doi: 10.1086/657321 [published Online First: 2010/11/12]
7. Nowak RG, Gravitt PE, Morrison CS, et al. Increases in human papillomavirus detection during early HIV infection among women in Zimbabwe. *J Infect Dis* 2011;203(8):1182-91. doi: 10.1093/infdis/jiq172 [published Online First: 2011/04/01]
8. Dames DN, Blackman E, Butler R, et al. High-risk cervical human papillomavirus infections among human immunodeficiency virus-positive women in the Bahamas. *PloS one* 2014;9(1):e85429. doi: 10.1371/journal.pone.0085429 [published Online First: 2014/01/28]
9. Looker KJ, Ronn MM, Brock PM, et al. Evidence of synergistic relationships between HIV and Human Papillomavirus (HPV): systematic reviews and meta-analyses of longitudinal studies of HPV acquisition and clearance by HIV status, and of HIV acquisition by HPV status. *Journal of the International AIDS Society* 2018;21(6):e25110. doi: 10.1002/jia2.25110 [published Online First: 2018/06/07]
10. Dartell MA, Rasch V, Iftner T, et al. Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative Tanzanian women. *International journal of cancer* 2014;135(4):896-904. doi: 10.1002/ijc.28712 [published Online First: 2014/01/07]
11. Linde DS, Korsholm M, Katanga J, et al. One-way SMS and healthcare outcomes in Africa: Systematic review of randomised trials with meta-analysis. *PloS one* 2019;14(6):e0217485. doi: 10.1371/journal.pone.0217485 [published Online First: 2019/06/07]
12. Akarolo-Anthony SN, Famooto AO, Dareng EO, et al. Age-specific prevalence of human papilloma virus infection among Nigerian women. *BMC public health* 2014;14:656. doi: 10.1186/1471-2458-14-656 [published Online First: 2014/06/29]
13. Guan P, Howell-Jones R, Li N, et al. Human papillomavirus types in 115,789 HPV-positive women: a meta-analysis from cervical infection to cancer. *International journal of cancer* 2012;131(10):2349-59. doi: 10.1002/ijc.27485 [published Online First: 2012/02/11]
14. Edna Omar V, Orvalho A, Nalia I, et al. Human papillomavirus prevalence and genotype distribution among young women and men in Maputo city, Mozambique. *BMJ open* 2017;7(7):e015653. doi: 10.1136/bmjopen-2016-015653 [published Online First: 2017/07/19]
15. Husain RS, Ramakrishnan V. Global Variation of Human Papillomavirus Genotypes and Selected Genes Involved in Cervical Malignancies. *Annals of global health* 2015;81(5):675-83. doi: 10.1016/j.aogh.2015.08.026 [published Online First: 2016/04/03]
16. Ogembo RK, Gona PN, Seymour AJ, et al. Prevalence of human papillomavirus genotypes among African women with normal cervical cytology and neoplasia: a systematic review and meta-analysis. *PloS one* 2015;10(4):e0122488. doi: 10.1371/journal.pone.0122488 [published Online First: 2015/04/16]
17. Bruni L AG, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S ICO/IARC. Information Centre on HPV and Cancer (HPV Information Centre). Human Papillomavirus and Related Diseases in Tanzania. Summary Report 17 June 2019
18. Organization WH. Human papillomavirus (HPV) and cervical cancer. 2019. https://www.who.int/en/news-room/fact-sheets/detail/human-papillomavirus-(hpv)-and-cervical-cancer.
19. Bosch FX, Munoz N. The viral etiology of cervical cancer. *Virus research* 2002;89(2):183-90. [published Online First: 2002/11/26]
20. Kelly HA, Ngou J, Chikandiwa A, et al. Associations of Human Papillomavirus (HPV) genotypes with high-grade cervical neoplasia (CIN2+) in a cohort of women living with HIV in Burkina Faso and South Africa. *PloS one* 2017;12(3):e0174117. doi: 10.1371/journal.pone.0174117 [published Online First: 2017/03/24]

21. Adebamowo SN, Dareng EO, Famooto AO, et al. Cohort Profile: African Collaborative Center for Microbiome and Genomics Research's (ACCME's) Human Papillomavirus (HPV) and Cervical Cancer Study. *International journal of epidemiology* 2017;46(6):1745-45j. doi: 10.1093/ije/dyx050 [published Online First: 2017/04/19]
22. Dartell M, Rasch V, Kahesa C, et al. Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study. *Sexually transmitted diseases* 2012;39(3):201-8. doi: 10.1097/OLQ.0b013e31823b50ad [published Online First: 2012/02/18]
23. Watson-Jones D, Baisley K, Brown J, et al. High prevalence and incidence of human papillomavirus in a cohort of healthy young African female subjects. *Sexually transmitted infections* 2013;89(5):358-65. doi: 10.1136/sextrans-2012-050685 [published Online First: 2013/03/15]
24. Houlihan CF, Baisley K, Bravo IG, et al. Rapid acquisition of HPV around the time of sexual debut in adolescent girls in Tanzania. *Int J Epidemiol* 2016;45(3):762-73. doi: 10.1093/ije/dyv367 [published Online First: 2016/03/06]
25. Baisley KJ, Andreasen A, Irani J, et al. HPV prevalence around the time of sexual debut in adolescent girls in Tanzania. *Sex Transm Infect* 2019 doi: 10.1136/sextrans-2019-054012 [published Online First: 2019/06/22]
26. Koliopoulos G, Nyaga VN, Santesso N, et al. Cytology versus HPV testing for cervical cancer screening in the general population. *The Cochrane database of systematic reviews* 2017;8:Cd008587. doi: 10.1002/14651858.CD008587.pub2 [published Online First: 2017/08/11]
27. Linde DS, Andersen MS, Mwaiselage JD, et al. Text messages to increase attendance to follow-up cervical cancer screening appointments among HPV-positive Tanzanian women (Connected2Care): study protocol for a randomised controlled trial. *Trials* 2017;18(1):555. doi: 10.1186/s13063-017-2215-x [published Online First: 2017/11/23]
28. Linde DS, Rasch V, Mwaiselage JD, et al. Competing needs: a qualitative study of cervical cancer screening attendance among HPV-positive women in Tanzania. *BMJ open* 2019;9(2):e024011. doi: 10.1136/bmjopen-2018-024011 [published Online First: 2019/03/02]
29. Linde DS AM, Mwaiselage JD, Manongi R, Kjaer SK, Rasch V. One-way text messages versus no text messages on attendance to follow-up cervical cancer screening among HPV-positive Tanzanian Women (Connected2Care): a parallel-group randomized controlled trial. *JMIR Preprints* 15/08/2019:15863 doi: DOI: 10.2196/preprints.15863
30. Bakiewicz A, Rasch V, Mwaiselage J, et al. "The best thing is that you are doing it for yourself" - perspectives on acceptability and feasibility of HPV self-sampling among cervical cancer screening clients in Tanzania: a qualitative pilot study. *BMC women's health* 2020;20(1):65. doi: 10.1186/s12905-020-00917-7 [published Online First: 2020/04/03]
31. Katanga J, Kjaer SK, Manongi R, et al. Performance of careHPV, hybrid capture 2 and visual inspection with acetic acid for detection of high-grade cervical lesion in Tanzania: A cross-sectional study. *PloS one* 2019;14(6):e0218559. doi: 10.1371/journal.pone.0218559 [published Online First: 2019/06/20]
32. Linde DS, Andersen MS, Mwaiselage J, et al. Effectiveness of One-Way Text Messaging on Attendance to Follow-Up Cervical Cancer Screening Among Human Papillomavirus-Positive Tanzanian Women (Connected2Care): Parallel-Group Randomized Controlled Trial. *Journal of medical Internet research* 2020;22(4):e15863. doi: 10.2196/15863 [published Online First: 2020/04/03]
33. McHome BL, Kjaer SK, Manongi R, et al. HPV types, cervical high-grade lesions and risk factors for oncogenic human papillomavirus infection among 3416 Tanzanian women. *Sex Transm Infect* 2020 doi: 10.1136/sextrans-2019-054263 [published Online First: 2020/04/10]
34. Cervical cancer prevention guidelines for low-resource settings. Available: http://resources.jhpiego.org/system/files/resources/cecap_trainer_0.pdf. 2011
35. Dartell M, Rasch V, Munk C, et al. Risk factors for high-risk human papillomavirus detection among HIV-negative and HIV-positive women from Tanzania. *Sexually transmitted diseases* 2013;40(9):737-43. doi: 10.1097/olq.0000000000000005 [published Online First: 2013/08/21]
36. Paul D. Blumenthal NM. Cervical Cancer Prevention Guidelines for Low-Resource Settings 2007: Jhpiego; 2005 [Available from: http://reprolineplus.org/system/files/resources/CeCaPfullmanual.pdf.
37. Nayar R, Wilbur DC. The Pap Test and Bethesda 2014. "The reports of my demise have been greatly exaggerated." (after a quotation from Mark Twain). *Acta Cytol* 2015;59(2):121-32. doi: 10.1159/000381842 [published Online First: 2015/05/23]
38. Xu L, Padalko E, Ostrbenk A, et al. Clinical Evaluation of INNO-LiPA HPV Genotyping EXTRA II Assay Using the VALGENT Framework. *Int J Mol Sci* 2018;19(9) doi: 10.3390/ijms19092704 [published Online First: 2018/09/14]

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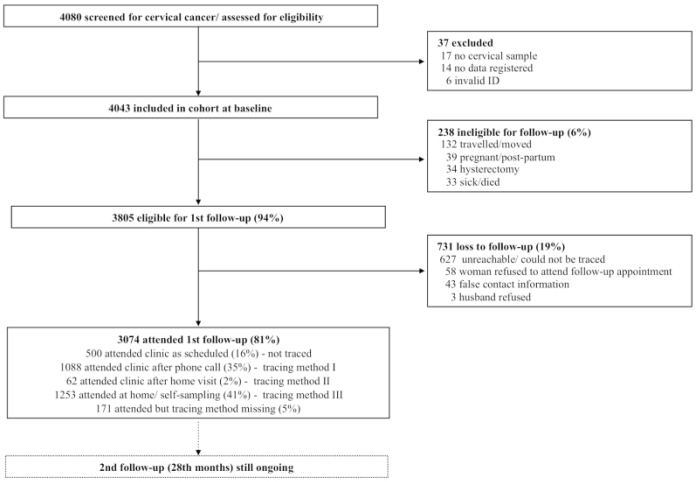

Flow chart

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Appendix A: Project Description

Comprehensive Cervical Cancer Prevention in Tanzania (CONCEPT)

1. Project Summary

The natural history of Human papillomavirus (HPV) in sub-Saharan Africa is not yet fully understood. As persistent HPV infection is a necessary factor in development of cervical cancer – a major health problem in sub-Saharan Africa - information about how HIV together with other risk factors interacts with HPV acquisitionand HPV persistence/clearance is warranted. Additionally, concern prevails about the quality of cervical cancer preventive strategies in sub-Saharan Africa. Against this background the project aims to provide a better understanding of the natural history of HPV with a view to HIV status, to measure the impact of a novel and simple screening method based on *Care*HPV testing and to assess how continuity of care among women who are tested HPV positive can be improved. The study will be linked up with the existing cervical cancer screening program at Ocean Road Cancer Institute (ORCI) and Kilimanjaro Christian Medical Centre (KCMC); and will include 4000 women who are attending screening service or HIV care and treatment. HPV acquisition and persistence/clearance patterns as well as the absolute risk of severe cervical precancerous lesions will be determined through a follow up study lasting 28 months. The test performance of *Care*HPV testing, liquid-based cytology and VIA will be described and the operating characteristics of the three screening methods will be assessed according to HIV status. Finally, the impact of a mobile phone intervention and a patient navigation model will be assessed and compared according to the proportion of HPV positive women who return for follow-up examinations. Additionally, the project will implement a research capacity building component focusing on transfer of knowledge and technology as well as training of PhD students. The activities will be carried out as five sub-studies: i) HPV acquisition pattern; ii) HPV persistence/clearance pattern; iii) Test performance of *Care*HPVtesting, liquid-based cytology and VIA; iv) Continuity of care among screened positive women and v) research capacity building as well as transfer of knowledge and technology

2. Objectives

With the overall aim of substantially improving cervical cancer prevention in Tanzania and thereby reduce mortality, the CONCEPT project focuses onthe natural history of human papillomavirus (HPV), which is the most important risk factor for cervical cancer.

HPV can take the form of being either a transient infection, that relatively rapidly is cleared by the host immune system or it can becomea persistent infection that may progress to high-grade cervical lesions or cervical cancer**(Fig. 1)**.In spite of the fact that cervical cancer is the most common malignancy among women in Sub-Saharan Africa (1), little is known about the distribution of HPV types, risk factors of incidence and patterns of persistence for different HPV types. The proposed project will address this lack of knowledge and provide new information about the natural history of HPV and consequences of HPV infection among HIV positive and HIV negative women.In addition, there is concern about the performance of the screening approaches applied in many sub-Saharan African countries and information on the quality of novel, affordable screening approaches that will perform well in remote areas iswarranted. Finally, in many sub-Saharan African settingsworries prevail about lack of continuity of care among women who are diagnosed with precancerous lesionsand therefor relevant treatment is not always offered. The proposed project will address these shortcomings in cervical cancer prevention. The researchwill build on the resultspreviously obtained by our research team(2-6) and will be innovative in the way that it through a comprehensive approach will use thenatural history of HPV to identify opportunities to strengthening and further develop the existing screening program in Tanzania, with a particular view to the importance of HIV positivity. In addition, with the aim to bridge the gap in continuity of care among women diagnosed with precancerous lesions,the project will develop and test a reliable and sustainable communication system through a multidisciplinary approach, involving community education, social mobilization and use of cell-phones. Thus the proposed study has the potential to produce results with immediate public health impact.

The specific objectives of the project are:

1. To assess acquisition patterns and incidence of HPV infection with a specific focus on differences in HPV acquisition, distribution of HPV types and risk factors among HIV positive and HIV negative women

2. To assess persistence of high-risk HPV infection with a specific focus on whether there are differences in HPV persistence in relation to specific HPV types and differences in risk factors for HPV persistence among HIV positive and HIV negative women. In addition, it is the aim to examine the absolute risk of HSIL or worse in relation to both one time HPV positivity and HPV persistence while taking HIV status into account

3. To evaluate the performance ofSelf collected *Care*HPV testing, health provider collected HPV test, Pap smear (liquid-based cytology) and visual inspection with acetic acid (VIA) for detection of cervical precancerous lesions with a special view to test performance among HIV positive and HIV negative women.

4. To evaluate and compare two different interventions aiming at ensuring continuity of care among women who are tested HPV positive in terms of effect and costs, and to describe barriers for not adhering to the scheduled follow-up

5. To enhance research capacity and transfer of knowledge and technologythrough the training of PhD students and the involvement of a post-doctoral fellow

3. Project's methodology

Based on the experience and success of our previous study of HPV prevalence in Tanzanian women, the present study will be linked up with the existing cervical cancer screening program in Dar es Salaam and Kilimanjaro Region. To make sure that we will include enough HIV positive women into the study, we will oversample HIV positive women. This will be done through enrolment of women attending HIV care and treatment in the two study areas.A total of 4000 women will be enrolled at baseline in the study -3500 women from the two screening settings and 500 HIV positive women from two HIV care and treatment clinics. Based on our previous experience, amongthe 3500 women recruited from the screening settings, around 700 will be high-risk (HR)-HPV positive and nearly 350 women will be HIV positive(2). Among the 500 HIV positive women recruited from the HIV clinics, an estimated 250 women will beHPV positive(2). Hence, the total study sample of 4000 women will include an estimated 950 HPV positive and 850 HIV positive women.A power calculation was based on McNemars test in the situation where we compare two diagnostic tests (1: standard test (VIA)vs 2:new test (*Care*HPV)) where the outcome is sensitivity S_1 and S_2, respectively.Based on our previous studies in Tanzania (4) it is estimated that 180-200 women will have precancerous lesions at baseline (~true positive), and we assume a significance level of 5% and that the sensitivity of the standard test is S_1=30%. We will then with 80% power be able to detect a significant difference if the sensitivity of the new test is at least S_2=44%. As we anticipate *Care*HPV testing to have a much higher sensitivity, we will have sufficient power in the present study

An overview of the study design is outlined in **Fig. 2.** In principle the study comprises a baseline visit and 2 follow-up visits:

*At **baseline*** we will collect on all participating women a cervical sample for *Care*HPV testing, a novel and simple quick test for detection of HPV.We will also obtaina liquid-based cervical swab (ThinPrep) for cytology examination (subsequently prepared and diagnosedin Denmark), high-risk Hybrid Capture (HC2) testing (in Germany), and genotyping (PCR-based HPV testing in Germany). Following this, VIA will be done with 5% acetic acid. The Tanzanian staff will receive training (re-training) in sample collection and VIA before start of the study by national trainers according to IARC guidelines. In case of a positive cytology (HSIL or worse) the woman will be called in and will be treated according to the cervical cancer screening standard of care methods in Tanzania. Similarly, all VIA positive women will be treated according to the cervical cancer screening standard of care methods in Tanzania.Information on socio-economic characteristics, lifestyle factors and reproductive history will be recorded through a personal

interview, and blood samples for HIV testing will be obtained. Before the initiation of the study, the staff in Tanzania will receive training in *Care*HPV testing.The C*are*HPV (including currently known HR-HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68) will be tested within 14 days in Tanzania. At the ***first follow-up*****,** taking place 14 months after inclusion,a randomly selected sample of 500 women will be trained on self-collection of a cervical swab for HPV testing. Thereafter another cervical swab (ThinPrep) will be collected (on all study subjects in the 1st follow-up) by a trained health provider. At the ***second follow-up*****,** taking place 26 months after inclusion, a cervical swab (ThinPrep) will be obtained from each woman. Women who do not return to the clinic for first and second follow-up will be traced and visited at home and invited to attend the clinic for screening. If they do not wish to re-attend, they will be offered screening through a self-collected HPV sample.We anticipate a response rate in the 1st follow-up at 90% and a response rate in the 2nd follow-up at 80%. The anticipated follow-up rate is based on experiencesfrom previous follow-up studies in Tanzania(7).
The study is grouped in five work package according to the specific objectives:

Work package 1, Acquisition patterns of high-risk (HR) human papillomavirus (HPV) with a special view to HIV status: Among women testing HR-HPV negative at baseline (Fig. 2), all women testing HIV positive (~190 from the screening clinic and 250 from HIV clinics = 440 in total) as well a random sample of 560 HPV negative/HIV negative women will be invited to a new gynecological examination after 14 months (1st follow-up visit), where a health provider cervical swab (ThinPrep) sample on all women is taken.These sampleswill all be tested for HPV using HC2 and genotyping will be performed on the HPV positive samples. At the 2nd follow-up visit (at 26 months) a health provider taken cervical swab (ThinPrep) will be obtained. All samples from the 2nd follow-up will be sent to Denmark for establishment of a cytology diagnosis and the remaining material will be sent to Germany for HC2 testing and subsequent genotyping of the HPV positives.All cytology results and HPV results will be sent back to Tanzania. In case of a positive cytology (HSIL or worse) the woman will be called in and will be treated according to the cervical cancer screening standard of care methods in Tanzania.
Based on the literature (8) we estimate an HPV acquisition rate among the initially HPV negative women at 1st follow-up of around 10%, similarly an acquisition rare of 10% from the 1st to the 2nd follow-up. The association between HR-HPV acquisition and the women's age, life style characteristics, reproductive history and HIV status will be assessed.

Work package 2, Persistence patterns of high-risk HPV types and absolute risk of severe cervical lesions focusing on the importance of HIV status: Persistence/clearance patterns of HR-HPV will be determined among all women who are HR-HPV positive at baseline(Fig. 2) (~700 from the screening clinic and 250 from the HIV clinic i.e. ~950 in total). They will be invited for follow-up examinations and tested for HR-HPV after 14 and 26 months (1st and 2nd follow-up visit). For this group of women also a self-collected cervical swab will be obtained at the 1st follow-up in 500 randomly selected women. HPV genotyping will be performed among women who are HR-HPV positive during follow-up.Women who are persistently HPV positive for the same HPV type at enrolment and at 1st follow-up will be called in for a cytological examination at the respective clinic.Also in case of a positive cytology (HSIL or worse), the women will be called in for further follow-up. HR-HPV persistence/clearance patterns will be described in relation to the women's age, life style characteristics, reproductive history, HIV status and HPV genotype. We estimate a persistence rate of 40% after 14 months and of 20% after 26 months (9). Due to the fact that a cytology diagnosis is obtained on all women at the 2nd follow-up, we will also be able to look at the absolute risk of HSIL or worse in relation to both one time HPV positivity, HPV persistence and according to HIV status.

Work package 3, Test performance of *Care*HPV testing, pap smear and VIA for detection of cervical precancerous lesions: As described above, all 4000 women enrolled will be screened by use of *Care*HPV testing, Pap smear (liquid based cytology i.e. ThinPrep) and VIA at the study baseline, and the sensitivity and specificity of *Care*HPV testing and VIA will be estimated and the positive and negative predictive values calculated. The operating

characteristics of the two screening methods will be assessed according to HIV status. All VIA positive women will subsequently be treated in agreement with thecervical cancer screening standard of care methods in Tanzania. In case of a positive cytology that was not already identified through a positive VIA, the women will be called in for further follow-up.High-quality cervical liquid-based cytology and where possible also cervical biopsies will be used as Gold Standard. Based on the samples collected at the 1st follow-up, the HPV results from the self-collected brush and the health provider collected brush will be compared.

Work package 4, Continuity of care among women who are tested are HPV positive – a comparison of two different interventions: Women who are tested HPV positive at enrolment will be randomized to either a patient navigation model or a cell phone model consisting of automated SMS messages. *Patient navigation model*: A trained community health worker will be identified as the woman's patient navigator. There will be established a one-to-one relationship between the patient navigator and the woman to address anticipated barriers such as communication difficulties and difficulties with arranging transportation. *Cell phone model***:** HPV positive women will receive automatically generated SMS messages, which will convey HPV result, send appointment reminders and health information during the first 12-14 months follow-up period.After 20 months, the continuity of care, based on the number of HPV positive women who return for the 1st follow-up examination after 14 months, will be compared. Additionally, the average time spent providing navigation from an HPV positive result is established to 12-14 months after and the associated cost will be calculated. Likewise the price of establishing and maintaining the system generating the SMS reminders will be measured. The differences in total costs and re-attendance between patient navigation and SMS reminders will be calculated. Re-attendance will be defined as HPV positive woman who re-attend within 12-14 months after the HPV positive result is established. Finally**,** HPV positive women who do not re-attend for screening after 12-14 months will be traced and interviewed. A mixed method approach, relying on structured questionnaires, in-depth interview and key informant interviews will be used to describe perceived barriers for attending 12-14 months follow-up.

Work package 5, Health service capacity building for cervical cancer prevention:Health service capacity building will be performed at primary, secondary and tertiary level. At the primary and secondary levels, key barriers for optimal use of existing communication paths for ensuring continuity of care among women diagnosed with precancerous lesions will be identified through a register based desk study. Based on the results, interview guides will be developed for in-depth interviews with health providers working at primary and secondary level and community representatives. The experiences from this assessment will be used to develop a training program in cervical cancer prevention and patient navigation that will include staff at primary and secondary health units together with community health workers in Dar es Salaam and Kilimanjaro Region. The trained community health worker will be employed as patient navigators. At tertiary level, the project will respond to the research needs set forth by ORCI and KCMC. Three PhD courses, one in Clinical Trials, one in Prevention and Control of Gynaecological Cancers and one in Policy Brief Writing will be offered at KCMC in alignment with the exiting BSU initiatives at KCMC. The PhD courses will be co-developed and co-taught by Tanzanian and Danish researchers. At both ORCI and KCMC there is a need to strengthen the capacities of researchers to undertake in-country PhD training at an international level. To address this need, four PhD studies, three Tanzanian and one Danish (co funded by SDU), will be included in the project. The Tanzanian PhD students will be recruited through public announcement of the scholarships and competitive applications.Two of the Tanzanian PhD students will be enrolled at KCMC and one at ORCI. Theywill additionally conduct 3 months of academic work each year in Denmark. The project will be performed as a twinning arrangement where the Tanzanian and the Danish PhD students will work closely together. To increase the expertise within HPV epidemiology and HPV testing in Tanzania and thereby increase the sustainability of the project outcomes, a post-doctoral fellow, Crispin Kahesa(CK), who has obtained his PhD as part of our previous research (2-6, 9) and who is presently acting as national trainer for the cervical cancer

prevention program in Tanzania, will be employed in the project. He will be visiting Institute of Medical Virology at Tuebingen University in Germany to get detailed knowledge about HPV testing and HPV analyses. In addition, to enhance local expertise in cervical cancer screening and HPV testing, a faculty exchange to the International Agency for Research on Cancer (IARC) in Lyon will also be arranged. Finally, to further upgrade CK's academic skills he will be involved as a co-supervisor of the two PhD projects focusing on Cervical Cancer Screening and Continuity of Care and write two independent papers based on the research findings.

Ethical research permissions will be obtained from the Ministry of Health in Tanzania and from local authorities in Dar es Salaam and Kilimanjaro. Ethical clearance will be obtained from the Ethical Review Board at KCMC and ORCI as well as from the Ethical Review Board of the National Institute of Medical Research. The project will follow the international ethical guidelines developed by CIOMS (Council for International Organization of Medical Sciences), placing particularemphasis on ensuring participant safety. Hence, women who have a positive cytology (HSIL or worse) will be called in and treated according to Tanzanian standard of care. Similarly, women who are persistently HPV positive will be traced, and liquid-based cytology samples will be obtained and analyzed. In case of a positive cytology result (HSILor worse), the women will be offered colposcopy directed biopsies and treatment according to the cervical cancer screening national guidelines. Informed written consent will be obtained from research participants and confidentiality guaranteed.The trial will be registered at ClinicalTrials.gov and trial analyses and reports will be made in accordance with CONSORT requirements. It is an important part of the study that all women will have a cytology examination when they exit the study after 26 months and we will make sure that all women are cared for in the best possible way.

4. Expected outputs and outcomes

The project will produce 4 PhD theses, at least 14 scientific papers published in international, peer-reviewed journals, at least 5 articles published in popular journals/magazines, at least 6 conference papers (4 national and 2 international), and a minimum of 12 research updates and policy briefs.

The expected outcomes of the project are:

- New knowledge about the natural history of HPV infection and consequences of HPV infection among HIV positive and HIV negative women
- New approaches in performing cervical cancer screening. On the basis of the research, possibleimprovements of the screening program will be identified, with a particular viewto implementation of HPV testing and improved continuity of care.
- A cadre of health staff and community health workers who are trained in cervical cancer control and prevention and who through an improved communication line will help facilitate on-going care and treatment to women who are screened positive
- Improved capacities among researchers to conduct interdisciplinary and internationally informed research on primary and secondary prevention of cervical cancer
- Decreased mortality from cervical cancer due to detection of precancerous lesions and earlier detection of cervical cancer
- Reduced poverty through enhancement of women's sexual and reproductive health. To a high degree cervical cancer is diagnosed in women at reproductive age and is thus leading to high numbers of premature deaths with substantial social and economic consequences at an individual level and in society. Prevention of cervical cancer will therefore have an impact on reduction of poverty and sustainable development in society.

5. Relevance

In Tanzania, cervical cancer is the commonest type of cancer in women, and that with the highest mortality rate. Annually, approximately 7300 new cases are diagnosed and about 4200women die from cervical cancer(11). Thus cervical cancer is a public health problem that has enormous social and economic population impact as it often affects women at reproductive

age(12). To address this public health problem, the project will provide new and important information on the natural history of HPV and how it relates to HIV, information that will be of help in the development of more efficient vaccines and screening strategies that targets HIV positive and HIV negative women. The project also aims to evaluate *Care*HPV testing (a simple to do test) as a tool for cervical cancer screening and to examine how continuity of care of women who are screened positive can be improved by two simple low cost interventions. The information generated from the project will help inform the future screening strategy in Tanzania as well as in other countries with high HIV prevalence. We will make it a priority that beside the publication of our results in scientific journals, we will communicate the results to decision makers, stakeholders and to the general population.The focus areas of our research, HPV, HIV and cervical cancer are well in line with the "Tanzanian National Health Research Policy" from 2013 that lists Communicable diseases, Non-communicable diseases and Reproductive health as top-three priority areas. Our research areas are also aligned with the Tanzanian Health Sector Strategic Plan III (HSSP III 2009-2015), supported by Danida, which also lists reproductive health and communicable and non-communicable diseases as priority areas. The project does also have relevance in relation to overall objectives and priorities of Danish development cooperation as expressed in The Right to a Better Life which states that "Denmark will be at the forefront of international efforts to promote sexual and reproductive health and rights, and in the fight against HIV/AIDS". Finally, through the linkage with KCMC, the activities are also in line with Danida priorities for research capacity building, since KCMC is one of the core institutions in the Building Stronger University (BSU) program.

6. Project plan

Since the project plan is complex and dynamic with interactions between multiple WPs, the key priorities will be to facilitate the necessary interactions between the WPs and to maintain the overall scientific direction over the life of the project. The project will start in January 2015 and end in December 2019. The existing ORCI and KCMC institutional bank accounts will be used for the project; and the existing financial and procurement regulations will be used for implementing the project in Tanzania. The main project milestones and timetable are shown on **Fig. 3**. The detailed budget is attached in the main application and it shows how the resource allocation in the project will be distributed between the institutions involved over the project period.

7. Participants, organization and management

Julius Mwaiselage is a medical doctor and epidemiologist and public health specialist. He is the Director of Cancer Prevention Services at ORCI. He has 9 years experiences in cancer epidemiological research in Tanzania and has been involved in various collaborative research projects focusing on HPV prevalence, cervical cancer screening and HPV vaccine introduction in Tanzania. He has authored more than 20 scientific papers in peer-reviewed journals and supervised 3 PhD students and more than 15 master's students. **Vibeke Rasch** is a gynaecologist and professor in global reproductive health. She has almost20 years experiences in reproductive health research in Tanzania, has acted as principal responsible party in an enhancing research capacity building project in Vietnam and has been member of the BSU steering committee. She has authored more than 100 scientific publications and supervised 16 PhD students, more than half from sub-Saharan Africa and Asia. **Susanne Krüger Kjær** is a medical doctor and professor of cancer epidemiology. Her main research areas are HPV and cancer and the importance of gene-environment interactions in cancer development with a focus on clinical utility and the translational aspect. She has authored more than 350 scientific papers, and she is the Danish primary investigator on the clinical, randomised trials of the efficacy of HPV vaccination. She has supervised more than 25 Phd students. **TwalibNgoma** is a professor of oncology. He has more than 25 years of experience in teaching, clinical work and research related to cancer. He is the executive director of ORCI and the head of clinical oncology department of Muhimbili University College of Health and Allied Science. **RachelManongi** is Head of Community Medicine Department at KCMC, she has a record of community based research with a special focus on HIV prevention and sustainable health promotion and has also been active in the establishment of a cervical cancer registry at KCMC. She has authored more than 40 papers in international journals.

The project builds on and extends existing collaboration between these Tanzanian and Danish researchers. The involved Danish researchers have solid experience in research capacity building in Tanzania and in HPV research and both have strong publication records. The proposed project will be undertaken in close coordination with the research capacity building activities conducted within the BSU initiative. The overall responsibility for the project lies with the main Tanzanian applicant. To facilitate cross-country project management, a Steering Board will be established between Tanzanian and Danish collaborators. A project management unit(PMU) will be established at ORCI. The PMU will consist of a project secretary and an accountant and will be responsible for day-to-day activities. To monitor the activities, a web-based project management tool will be established. The web tool will include detailed updated work plans linked to the work packages so partners can track project progress. Project documents will be available on the web-site. Members of the Steering Board will meet on a regular basis to ensure a continuous progress of the study. In addition, annual workshop meetings will beheld with representatives from the partner institutions.

8. Project's international dimension

There is a great international interest in cervical cancer prevention focusing on different screening modalities, HPV testing and HPV vaccination, and it is one of the areas where substantial progress has been made in recent years and it is also one of the areas where research has the greatest translational potential. The suggested project relies heavily on collaboration between researchers in Tanzania, Denmark, Germany and France who have strong expertise in HPV epidemiology, HPV testing technology, cervical cancer screening approaches, and international health. Through this international collaboration, we will obtain a strong and valuable synergy. By means of this project there will be a great opportunity for transfer of knowledge and technology to Tanzania, which in a longer perspective may be further transferred to neighbouring sub-Saharan African countries with similar high prevalence rates of HPV and HIV.

9. New knowledge

Virtually all cases of cervical cancers and high-grade precursor lesions are caused by a persistent infection with HPV(13). Although effective prophylactic vaccines against HPV have been developed, they are still relatively expensive and logistically demanding as they currently require a 3-dose regimen. Furthermore, they do not treat already existing HPV infections and related diseases. Several African cross-sectional studies of the prevalence of HPV have been performed, including our own from Tanzania where we found an HPV prevalence of 20.1% among 3700 women(2). In the same study we found that 9.3% of the women were HIV positive. In contrast, only few prospective studies on HPV epidemiology have been conducted in Africa. Of these, some had a limited sample size (14), some did only include HIV negative women(9) or exclusively used self-sampled cervical swabs(15). In spite of the fact that cervical cancer is the most common malignancy among women in Sub-Saharan Africa(1), little is known about the distribution of HPV types, independent risk factors of incidence and patterns of persistence for different HPV types. Even though HPV16 has been found to be common in sub-Saharan African women, some studies have reported HPV52 and HPV58 to be more prevalent(2). Data on which HPV types are more likely to persist in relation to HIV status are scarce, particularly in HIV positive individuals. Results from the proposed study will add important information to our knowledge about the natural history of HPV in an HIV high-risk area and will be helpful in tailoring screening programs to match the needs of HIV positive and HIV negative women.

The conventional cytology screening (Pap smear followed by colposcopically-directed biopsies) demands costly cytology laboratories with skilled and highly experienced personnel, and multiple visits at regular intervals are needed. Consequently, the Pap smear screening is neither sufficiently developed nor sustainable in less developed countries(16). Therefore, cost effective methods such as VIA have been adopted in several countries for early detection of precancerous lesions. In 2002 cervical cancer screening based on VIA was implemented at

ORCI and the program has subsequently been scaled up to cover other regions in Tanzania. However, several studies, including our own recent study, have found VIA to have a limited sensitivity(4). In contrast, HPV screening is appealing due to a higher sensitivity and a higher negative predictive value(17). However, successful HPV screening in countries with limited resources requires a simple HPV test that will perform well also in remote areas and which is affordable. Finally, self-sampling will most likely be needed to make screening practical in some settings. . In relation to these issues, our study will contribute new knowledge which can immediately be used and implemented to the benefit of the women.

A successful programme for cervical cancer prevention requires function in its entirety. The programme should ensure high levels of screening coverage of the target population, offer high quality services, have good referral systems that guarantee patient follow-up and make certain that women receive appropriate treatment. Experiences from Tanzania mainland have documented that these preconditions are often not adhered to due to a poor functioning health system and as a consequence the screening results are often not conveyed and proper action not always taken. Currently, there is no mechanism in place in Tanzania to help women navigate between the potential barriers, which may be hindering factors for obtaining confirmatory diagnosis and adequatetreatment of cervical precancerous lesions. Mobile Health, which implies the use of mobile communication devices for health care, is seen as a complementary strategy for strengthening health systems and the use of SMS has successfully been used to remind patients to take drugs and attend appointment e.g.in Kenya(18). Similarly, members of our research team have documented the effect of SMS on antenatal care attendance and skilled delivery attendance in Tanzania(7).The Patient Navigation Model is an alternative approach to enhance continuity of care among underserved populations. The navigators can be trained community health workers or peer educators who provide support and guidance (19). Patient navigation is used as a standard of care in most of Western oncological departments and has been proven to be successful in several studies e.g: Cancer control among urban African American (20) and Breast cancer screening(21). Understanding the acceptance of these two proposed models among Tanzanian women detected to have HPV will help health care professionals to develop more effective continuum of care programs by promoting attendance to HPV screening and follow-up of disease progression.

10. Publication and dissemination strategy

The research findings will be communicated via a project website, scientific paper in peer-reviewed journals and popular articles. Further to get maximum impact of the findings, a stakeholder workshop focusing on cervical cancer screening and continuity of care will be held at the beginning and at the end of the project. The invitees will include Women's groups representatives, civil society, health care providers, health sector officials and researchers. The workshop will involve stakeholders in the formulation of intervention strategies, which will enhance continuity of care among women who are screened positive. Further, at the end of the project period a policy brief workshop facilitated by a communication expert will be held and will result in the formulation of a policy brief that summarizes the research findings and provides recommendations to decision makers. The policy brief will be produced and shared at a national dissemination seminar where health policy makers, Danida representatives and other relevant stakeholder are invited.

11. Strategy for phasing out of the project

The project will be undertaken in cooperation with Ministry of Health officials and with health system representatives. Based on the research conducted within each work package, concrete recommendations for improved cervical cancer prevention will be developed and shared with health policy makers and other stakeholders. Since the PI is Director of Cancer Preventive service in Tanzania at ORCI and a member of the Ministry of Health technical working group for cervical cancer prevention and control in Tanzania, he will ensure the recommendations of the project are sent to the respective authorities and implemented. Initially most of the technical recommendations from the project will be implemented at ORCI, KCMC and among cervical cancer screening implementing partners in Tanzania after update of the cervical cancer

screening national service delivery guidelines. Furthermore, through a phased and participatory approach, the policy recommendations for the Ministry of Health, will be discussed at the relevant level of authority in order to ensure the updated policy guidelines and ministerial circulars for cervical cancer include the project recommendations on improvement, particularly on continuity of care. The Tanzanian post-doctoral and PhD students will be in the forefront in the implementation and sustainability of the comprehensive cervical cancer prevention in Tanzania given the knowledge and skills obtained in the project; and it is anticipated that they will be employed by ORCI and KCMC or even at the Ministry of Health. The established cohort of HPV positive women will be kept and maintained at ORCI for future studies on HPV persistence and clearance patterns and women's absolute risk of subsequently developing precancerous lesions (17).

Fig. 1:Natural history of human papillomavirus (HPV) infection and cervical precancerous lesions

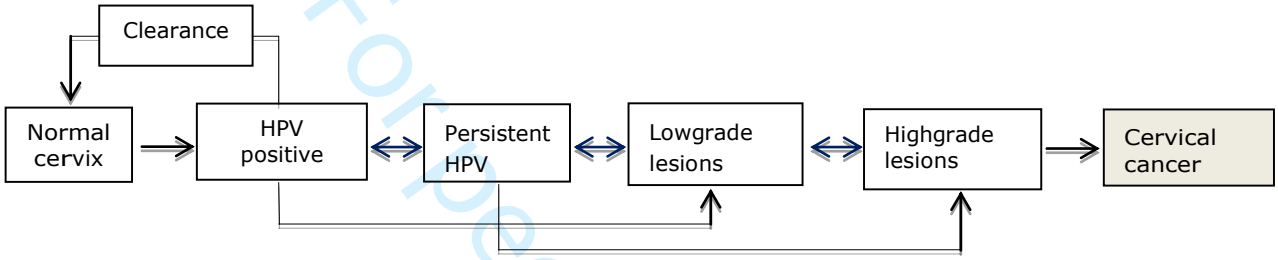


Fig 2: The schematic overview of the study design

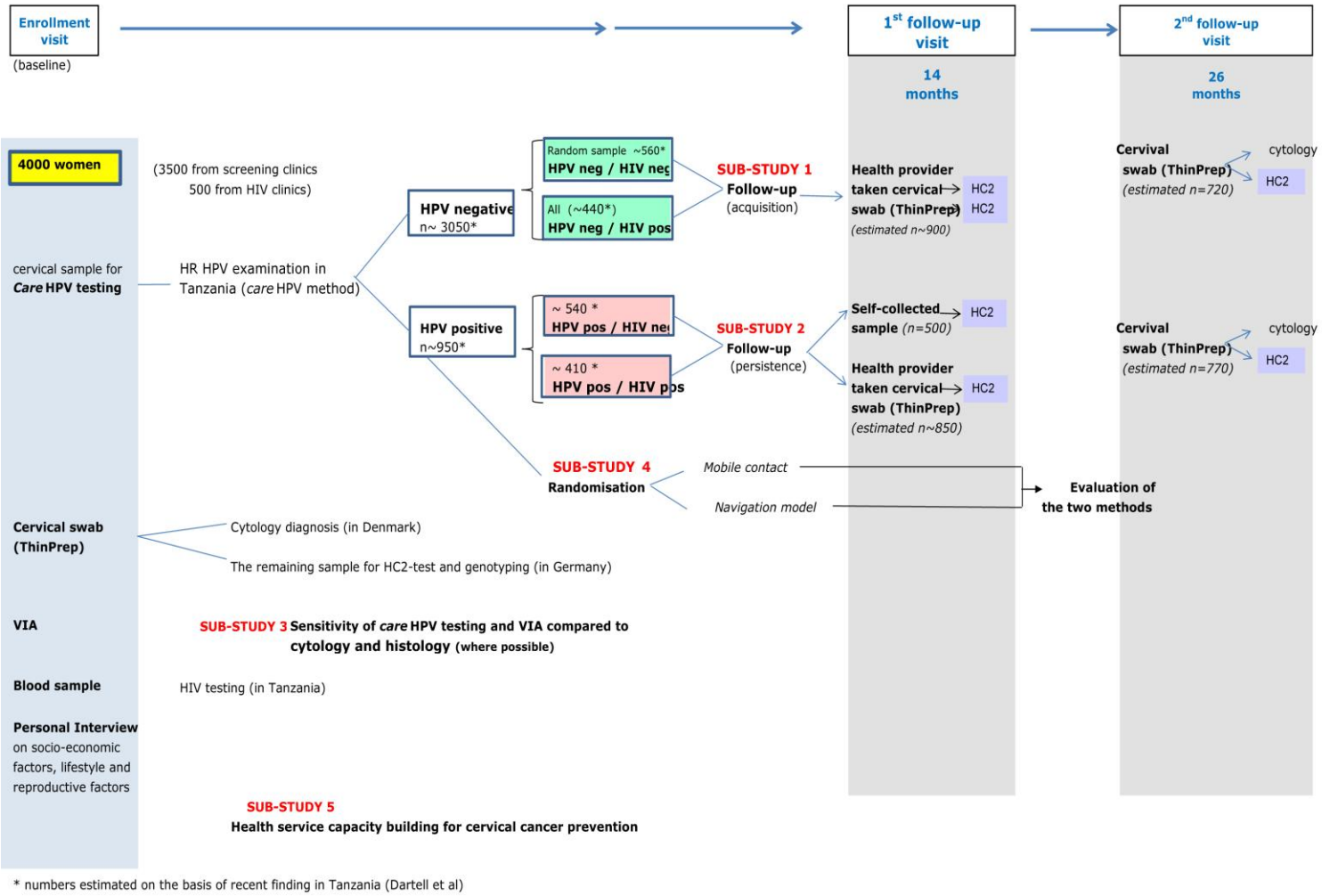
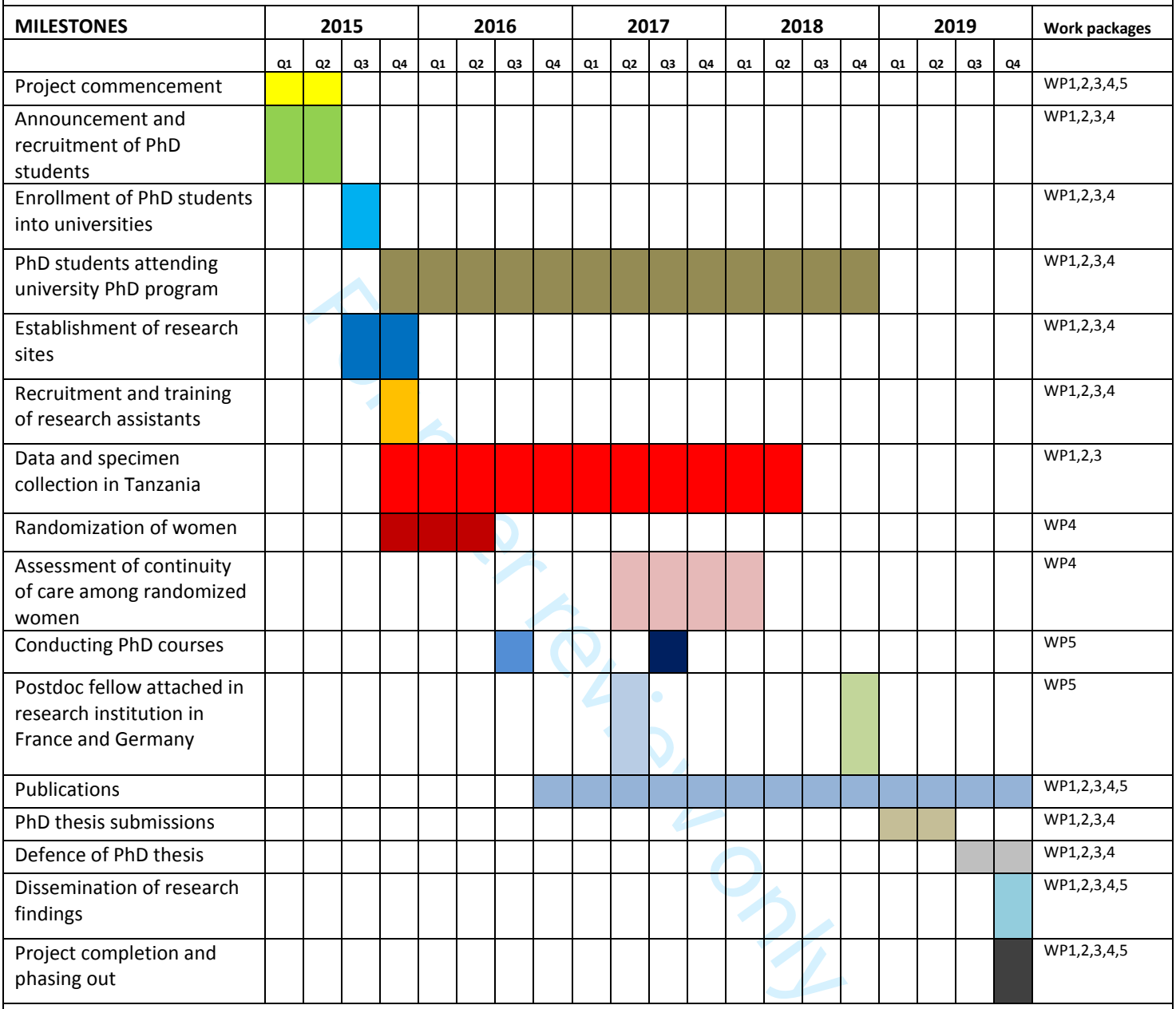


Fig 3: The schematic overview of the project milestones and timetable

FIG 3: THE SCHEMATIC OVERVIEW OF THE PROJECT MILESTONES AND TIMETABLE



Note: Project commencement involves planning meeting of researchers, setting up of the project office, and ensuring ethical clearance is obtained from relevant bodies

Note: Project completion involves writing of the final project report, final auditing of the project, phasing out of the project to ensure sustainability

12. Main References

1.**Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International Journal of Cancer 2010 Dec 15;127(12):2893-917.
2.**Dartell M**, Rasch V, Kahesa C, Mwaiselage J, Ngoma T, Junge J, et al. Human papillomavirus prevalence and type distribution in 3603 HIV-positive and HIV-negative women in the general population of Tanzania: the PROTECT study. SexuallyTransmittedDiseases. 2012 Mar;39(3):201-8.
3. **Dartell M**, Rasch V, Munk C, Kahesa C, Mwaiselage J, Iftner T, et al. Risk factors for high-risk human papillomavirus detection among HIV-negative and HIV-positive women from Tanzania. SexuallyTransmittedDiseases. 2013 Sep;40(9):737-43.
4. **Dartell MA**, Rasch V, Iftner T, Kahesa C, Mwaiselage JD, Junge J, et al. Performance of visual inspection with acetic acid and human papillomavirus testing for detection of high-grade cervical lesions in HIV positive and HIV negative Tanzanian women. International Journal of Cancer 2014 Jan 4. PubMed PMID: 24391021. Epub 2014/01/07. Eng.
5. **Kahesa C**, Kjaer S, Mwaiselage J, Ngoma T, Tersbol B, Dartell M, et al. Determinants of acceptance of cervical cancer screening in Dar es Salaam, Tanzania. BMC Public Health. 2012;12:1093.
6. **Kahesa C**, Kjaer SK, Ngoma T, Mwaiselage J, Dartell M, Iftner T, et al. Risk factors for VIA positivity and determinants of screening attendances in Dar es Salaam, Tanzania. BMC Public Health. 2012;12:1055. PubMed PMID: 23216752.
7. **Lund S**, Hemed M, Nielsen BB, Said A, Said K, Makungu MH, et al. Mobile phones as a health communication tool to improve skilled attendance at delivery in Zanzibar: a cluster-randomised controlled trial. BJOG 2012 Sep;119(10):1256-64. PubMed PMID: 22805598.
8. **Nielsen A**, Iftner T, Munk C, Kjaer SK. Acquisition of high-risk human papillomavirus infection in a population-based cohort of Danish women.Sexually Transmitted Diseases 2009 Oct;36(10):609-15.
9. **Fukuchi E**, Sawaya GF, Chirenje M, Magure T, Tuveson J, Ma Y, et al. Cervical human papillomavirus incidence and persistence in a cohort of HIV-negative women in Zimbabwe. Sexually Transmitted Diseases. 2009 May;36(5):305-11. PubMed PMID: 19295468.
10. **Olesen TB**, Iftner T, Mwaiselage J, Kahesa C, Rasch V, Ngoma T, et al. Prevalence and type distribution of human papillomavirus among 1813 men in Tanzania and the relationship to HIV status. Sexually Transmitted Diseases. 2013 Jul;40(7):592-8. PubMed PMID: 23965778. Epub 2013/08/24. eng.
11. Human Papillomavirus and Related Diseases in Tanzania. Summary Report [Internet]. ICO Information Centre on HPV and Cancer.
12. **Chokunonga E**, Borok MZ, Chirenje ZM, Nyakabau AM, Parkin DM. Trends in the incidence of cancer in the black population of Harare, Zimbabwe 1991-2010. International Journal of Cancer 2013 Aug 1;133(3):721-9. PubMed PMID: 23364833. Epub 2013/02/01. eng.
13. **Kjaer SK**, van den Brule AJ, Bock JE, Poll PA, Engholm G, Sherman ME, et al. Human papillomavirus--the most significant risk determinant of cervical intraepithelial neoplasia. International Journal of Cancer 1996 Mar 1;65(5):601-6.
14.**Veldhuijzen NJ**, Vyankandondera J, van de Wijgert JH. HIV acquisition is associated with prior high-risk human papillomavirus infection among high-risk women in Rwanda. AIDS (London, England). 2010 Sep 10;24(14):2289-92. PubMed PMID: 20613457. Epub 2010/07/09. eng.
15. **Safaeian M**, Kiddugavu M, Gravitt PE, Gange SJ, Ssekasanvu J, Murokora D, et al. Determinants of incidence and clearance of high-risk human papillomavirus infections in rural Rakai, Uganda. Cancer Epidemiology, Biomarkers &Prevention 2008 Jun;17(6):1300-7.
16. **Denny L**. Cytological screening for cervical cancer prevention. Best practice & research Clinical obstetrics & gynaecology. 2012 Apr;26(2):189-96. PubMed PMID: 22071306. Epub 2011/11/11. eng.
17. **Kjaer SK**, Frederiksen K, Munk C, Iftner T. Long-term absolute risk of cervical intraepithelial neoplasia grade 3 or worse following human papillomavirus infection: role of persistence. Journal of the National Cancer Institute. 2010 Oct 6;102(19):1478-88. PubMed PMID: 20841605.
18. **Lester RT**, Ritvo P, Mills EJ, Kariri A, Karanja S, Chung MH, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial. Lancet. 2010 Nov 27;376(9755):1838-45. PubMed PMID: 21071074.
19. **Honeycutt S**, Green R, Ballard D, Hermstad A, Brueder A, Haardorfer R, et al. Evaluation of a patient navigation program to promote colorectal cancer screening in rural Georgia, USA. Cancer. 2013 Aug 15;119(16):3059-66. PubMed PMID: 23719894.
20. **Halbert CH**, Briggs V, Bowman M, Bryant B, Bryant DC, Delmoor E, et al. Acceptance of a community-based navigator program for cancer control among urban African Americans. Health education research. 2014 Feb;29(1):97-108. PubMed PMID: 24173501.
21. **Lee JH**, Fulp W, Wells KJ, Meade CD, Calcano E, Roetzheim R. Patient navigation and time to diagnostic resolution: results for a cluster randomized trial evaluating the efficacy of patient navigation among patients with breast cancer screening abnormalities, Tampa, FL. PloS one. 2013;8(9):e74542. PubMed PMID:

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Response
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Indicated as Cohort in all appropriate sections
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Indicated in the section "abstract"
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Explanation provided in the "Introduction "section
Objectives	3	State specific objectives, including any prespecified hypotheses	These has been provided in ll. 33-34; 126-128
Methods			
Study design	4	Present key elements of study design early in the paper	Indicated in the sub section "study design and study population", ll. 131-180
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Indicated in the sub sections "study design and study population", ll. 131-180; "assessment of exposure, ll. 181-237; "outcome measures; ll. 239-248; "table 1: Overview of data collected in the CONCEPT cohort"
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Indicated in the sub sections "study design and study population", ll. 131-180; "assessment of exposure, ll. 181-237; "outcome measures; ll. 239-248;
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA - No matching was done
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Indicated in the sub sections "assessment of exposure, ll. 181-237; "outcome measures; ll. 239-248
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Description of this item has been provided in table 1 - Overview of data collection
Bias	9	Describe any efforts to address potential sources of bias	Indicated in the sub sections

			"assessment of exposure, ll. 181-237; "outcome measures; ll. 239-248
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	An overview of data management has been provided in the sub section "Data management", ll. 250-257. Detailed description of the statistical analysis may be provided in the respective individual articles.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	An overview of data management has been provided in the sub section "Data management", ll. 250-257. Detailed description of the statistical analysis may be provided in the respective individual articles.
		(*b*) Describe any methods used to examine subgroups and interactions	An overview of data management has been provided in the sub section "Data management", ll. 250-257. Detailed description of the statistical analysis may be provided in the respective individual articles.
		(*c*) Explain how missing data were addressed	Missing data for selected variables are described in Table 1 and Table 2.
		(*d*) If applicable, explain how loss to follow-up was addressed	Indicated in the sub sections "study design and study population", ll. 131-180.
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	This information has been provided in the flow chart, figure 1.
		(b) Give reasons for non-participation at each stage	This information has been provided in the flow chart, figure 1
		(c) Consider use of a flow diagram	Flow chart has been provided, figure 1

Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Relevant characteristics of the participants and their distribution has been provided in Table 2
		(b) Indicate number of participants with missing data for each variable of interest	Information on missing values has been provided for each variable in Table 2 & Table 3
		(c) Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Table 2 and 3 provide a measure of important events at a baseline and follow-up
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 3 provides Confidence interval of the important outcome measures at baseline and on follow up
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	NA. Cohort profile. However, summarized in “abstract”.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Indicated in the section “Strengths and limiations”, ll. 319-338.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	NA. Cohort profile
Generalisability	21	Discuss the generalisability (external validity) of the study results	Indicated in the section “Strengths and limiations”, ll. 319-338.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Inidicated in the section “financial disclosure, ll. 359-361.

*Give information separately for exposed and unexposed groups.

Study number

ConcepT

Comprehensive Prevention of Cervical Cancer in Tanzania

Study site: ORCI ☐ **KCMC** ☐ **MAGOMENI** ☐ **MAWENZI** ☐

Date _____ **Study number** _____

Health Provider Initials _____ **Participant initials** _____

BACKGROUND

1.

How old are you?	☐☐ years

2. Are you:

Married, monogamous	1 ☐
Married, polygamous	2 ☐
Cohabiting	3 ☐
Single, with regular partner	4 ☐
Single, no regular partner	5 ☐
Divorced/ Widow	6 ☐

How long have you known your husband / cohabiter / regular partner?

☐☐ years ☐☐ months

3. With whom are you presently living?

Husband / cohabiter	1 ☐
Parents	2 ☐
Parents in law	3 ☐
Other relatives	4 ☐
Friends	5 ☐
Nobody	6 ☐

4. What is the highest level of formal education you have completed?

No formal education	1 ☐
Standard 1-4	2 ☐
Standard 5-7	3 ☐
Form 1-4	4 ☐
Form 5-6	5 ☐
University/college	6 ☐
Other _____ **Specify**	8 ☐

5. What is your religion?

Christian	1 ☐
Muslim	2 ☐
Other _____ **Specify**	3 ☐

LIFESTYLE HABITS AND HEALTH

6. Do you smoke cigarettes?

Yes, every day	☐ 1
Yes, at least once a week	☐ 2
Yes, but less than once a week	☐ 3
No, but I previously smoked	☐ 4
No, never → (go to question 11)	☐ 5

7. How old were you, when you started to smoke cigarettes regularly?

(i.e. at least once a week)

age _____ years

8. How many years have you smoked cigarettes regularly? (subtract periods of smoking cessation)

number of years: _____

9. **If you are a current smoker, how much do you smoke on an average day?**

number of cigarettes: _____

10. **If you no longer smoke cigarettes, how old were you when you stopped smoking?**

age _____ years

11. **Have you ever drunk alcohol and if yes, how old were you when you started drinking alcohol?**

Have never been drinking	12 years or younger	13-14 years	15-16 years	17-18 years	19-20 years	21 years or older
☐ 1 (Go to question 14)	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

12. **How much per week do you usually drink of the following types of alcohol?**

Beer	No. of glasses per week on average	
Local brew	No. of drinks per week on average	
Wine	No. of glasses per week on average	
Liquor	No. of drinks per week on average	

(**1 bottle of vine** = 6 glasses, **1 bottle of liquor** = 20 drinks, **1 bottle of beer** = 2 glasses)

13. **How many times per month on average do you have more than 6 drinks on the same occasion?**

Never	Less than once a month	1-3 times per month	4-8 times per month	≥ 9 times per month
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

14. **How do you regard your own health?**

Excellent	Very good	Good	Less good	Bad
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

15. How do you perceive your body size?

Much too thick	A little too thick	Good	A little too thin	Much too thin
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

REPRODUCTIVE HEALTH and SEXUAL HABITS

16. Have you ever been pregnant?

- yes	1 ☐	
- no	2 ☐	→ **Go to question 17**

If yes:

Total number of pregnancies	1 ☐☐
Total number of births	2 ☐☐

How old were you at the first pregnancy? ☐☐ years

How old were you when you gave birth to your first child? ☐☐ years

17. Did you ever have a sexual partner?

- yes	1 ☐	
- no	2 ☐	**Go to question 21**

If yes:

How old were you at first intercourse? ☐☐ years

How old was your first partner at that time? ☐☐ years

18. How many sexual partners did you have during your lifetime? ☐☐ number

19. Did you have sexual intercourse within the last 12 months?

- yes	1 ☐
- no	2 ☐

If yes:

How often have you used condoms during the last 12 months?

At every sexual intercourse	1 ☐
Frequently but not at every intercourse	2 ☐
Rarely	3 ☐
Only sexual intercourse without condoms	4 ☐

20. Is your husband / cohabiter / regular partner circumcised?

Yes	1 ☐
No	2 ☐
No husband / cohabiter / regular partner	3 ☐

21. Has a doctor or other health care provider told you that you had genital warts (condyloma)?

- yes	1 ☐
- no	2 ☐

If yes:

How old were you when you had genital warts for the first time? ☐☐ years

Have you had genital warts in the last 12 months?

- yes	1 ☐
- no	2 ☐

22. Have you ever been screened against cervical cancer?

- yes	1 ☐
- no	2 ☐

If yes:

Has a doctor or other health care provider told you that you had precancerous lesions on the cervix?

- yes	1 ☐	
- no	2 ☐	**Go to question 23**

When did you have your last diagnose of precancerous lesions?

☐☐ calendar month ☐☐☐☐ calendar year

Which treatment did you receive?

- Cryo therapy	1 ☐
- LEEP	2 ☐
- Don't know	3 ☐

23. Has a doctor or other health care provider told you that you had one of the following sexually transmitted diseases?

Chlamydia	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years
Gonorrhea	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years
Syphilis	1 ☐ Yes	2 ☐ No	**If yes**	Age at first episode_____ Years

24. Have you ever been tested for HIV?

- yes	1 ☐
- no	2 ☐

If yes:

Have you ever tested positive?

- yes	1 ☐	
- no	2 ☐	**Go to question 25**

If yes:

When did you test positive? ☐☐ calendar month ☐☐☐☐ calendar year

When did you have your last CD4 count test?
(If more than 6 months ago → refer the woman for a new test)

☐☐ calendar month ☐☐☐☐ calendar year

What was the result of the CD4 count? _____number

Have you ever been started on ARV treatment?

- yes	1 ☐
- no	2 ☐

If yes:

				started when ?	
First line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year
Second line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year
Third line	1 ☐ Yes	2 ☐ No	**If yes**	calendar month	calendar year

What is your CTC card number? _____ Clinic name _____ Card number

What is your CTC file number? _____ File number

If you do not know, can we call you and get the number?

- yes	1 ☐
- no	2 ☐

TAARIFA KUHUSU SARATANI YA SHINGO YA KIZAZI
(KNOWLEDGE OF CERVICAL CANCER)

25. Sentensi zifuatazo zinahusu saratani ya shingo ya kizazi. Sema kweli au si kweli kwa kila sentensi

(Here are some statements about cervical cancer. I will ask you to answer which are true and which are false)

1. Malaria (mbu) inasababisha saratani ya shingo ya kizazi *(Malaria (mosquito) causes cervical cancer)*	Kweli ☐	Si kweli ☐
2. Kupata maumivu wakati wa kukojoa ni dalili ya saratani ya shingo ya kizazi *(Pain during urination can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
3. Saratani ya shingo ya kizazi ndiyo inayoongoza kwa magonjwa ya kanza za wanawake hapa Tanzania *(Cervical cancer is the most commen cancer disease among Tanzanian women)*	Kweli ☐	Si kweli ☐
4. Unaweza kupata saratani ya shingo ya kizazi kwa kubusiana *(You can get cervical cancer from deep kissing)*	Kweli ☐	Si kweli ☐
5. Inawezekana kujikinga na saratani ya shingo ya kizazi *(It is possible to prevent cervical cancer)*	Kweli ☐	Si kweli ☐
6. Kutokwa damu ukeni ni dalili kuu ya ugonjwa wa saratani ya shingo ya kizazi *(Vaginal bleeding is the most common sign of cervical cancer)*	Kweli ☐	Si kweli ☐
7. Jua kali linaweza kusababisha saratani ya shingo ya kizazi *(Too much sun can lead to cervical cancer)*	Kweli ☐	Si kweli ☐
8. Maambukizi ya kwenye shingo ya kizazi mara zote hubadilika kuwa saratani *(A cervical infection will always turn into cancer)*	Kweli ☐	Si kweli ☐
9. Wanawake wenye VVU wako kwenye hatari kubwa ya kupata saratani ya shingo ya kizazi *(HIV-positive women have higher risk of developing cervical cancer)*	Kweli ☐	Si kweli ☐
10. Saratani ya shingo ya kizazi mara nyingi hugundulika mapema kutokana na dalili zake (Cervical cancer is often found at an early stage due to obvious symptoms)	Kweli ☐	Si kweli ☐
11. Unaweza kupata saratani ya shingo ya kizazi kwa kujamiiana bila kinga *(You can get cervical cancer from unprotected sexual intercourse)*	Kweli ☐	Si kweli ☐
12. Kupima afya kunaweza kugundua maambukizi ya kwenye shingo ya kizazi na kuyazuia yasibalike kuwa saratani *(Screening can detect cervical infections so they do not develop into cancer)*	Kweli ☐	Si kweli ☐
13. Saratani ya shingo ya kizazi inaongoza kwa kusababisha vifo vinavyotokana na saratani kwa wanawake hapa Tanzania *(Cervical cancer is the main cause of cancer-related death among Tanzanian women)*	Kweli ☐	Si kweli ☐
14. Saratani ya shingo ya kizazi mara nyingi huwapata wanawake wakiwa kwenye miaka ya ishirini. *(Cervical cancer is most common for women in their 20's)*	Kweli ☐	Si kweli ☐
15. Kuwashwa ukeni kunaweza kuwa ni dalili ya saratani ya shingo ya kizazi *(Itchiness in the vaginal area can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
16. Kirusi kinachoitwa Human papilloma virus ndicho kisababishacho saratani ya shingo ya kizazi *(A virus called "Humanpapiloma virus" (HPV) causes cervical cancer)*	Kweli ☐	Si kweli ☐

UKUBALI WA UJUMBE MFUPI KUPITIA SIMU YA MKONONI
(ACCEPTANCE OF MOBILE MESSAGES)

UTANGULIZI *(Introduction):*
Kwenye utafiti huu wanawake watatakiwa kurudi baada ya miezi 14. Baadhi ya wanawake watatumiwa ujumbe kupitia simu ya mkononi wenye taarifa za afya na kukukumbusha siku ya kurudi kliniki. Nitakuuliza maswali machache kuhusu ujumbe wa kupitia simu ya mkononi

(In this study, all women will get a new appointment at the clinic after 14 months. However, some women will also receive health information and reminders of their appointment via sms. Here are some questions about mobile messages.)

26. Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au ya familia yako? (Chagua tabasamu sahihi kuonyesha utakavyojisikia)

(How do you feel about receiving health information and reminders of your appointment via sms on your or your family's mobile phone? Choose the one smiley that best shows how you feel)

Siipendi kabisa
I do not like it at all ☐

Siipendi
I do not like it ☐

Sio sawa
It is not okay ☐

Sawa
It is okay ☐

Naipenda
I like it ☐

Naipenda sana
I like it very much ☐

27. Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au ya familia yako? (Weka alama ya mstari wima kuonyesha utakavyojisikia).

(How do you feel about receiving health information and reminders of your appointment via sms on your or your family's mobile phone? Make one vertical mark on the line similar to how you feel)

Thanks a lot for your help

If there are any comments to add, please write them below

_____
Baseline Study number

_____
Follow-up Study number

ConcepT

Comprehensive Prevention of Cervical Cancer in Tanzania

FOLLOW-UP QUESTIONNAIRE

Study site: ORCI ☐ **KCMC** ☐ **MAWENZI** ☐

Date _____ **Follow-up Study number** _____

Baseline Study number_____

Health Provider Initials _____ **Participant initials** _____

REPRODUCTIVE HEALTH and SEXUAL HABITS

1. Have you given birth since your last screening visit?

- yes	1 ☐	
- no	2 ☐	→ **Go to question 2**

If yes:

Total number of pregnancies since last visit	1 ☐☐
Total number of births since last visit	2 ☐☐

2. Did you have a sexual partner since your last screening visit?

- yes	1 ☐	
- no	2 ☐	**Go to question 3**

If yes:

Have you had a *new* sexual partner since your last screening visit?

- yes	1 ☐
- no	2 ☐

How many sexual partners did you have since your last screening visit?

|__|__|__| number

How often have you used condoms since your last screening visit?

At every sexual intercourse	1 ☐
Frequently but not at every intercourse	2 ☐
Rarely	3 ☐
Only sexual intercourse without condoms	4 ☐

3. Is your husband / cohabiter / regular partner circumcised?

Yes	1 ☐
No	2 ☐
No husband / cohabiter / regular partner	3 ☐

Hormonal Family Planning

4. Have you ever used hormonal family planning methods?

- yes	1 ☐	
- no	2 ☐	**Go to question 5**

If yes:

What type of hormonal contraceptives have you used?

Type	No, never	Yes	If *yes*, how long have you used it overall?
Birth control pills	2 ☐	1 ☐	☐☐ years and ☐☐ months
Birth control shot (Depo-provera)	2 ☐	1 ☐	☐☐ years and ☐☐ months
Birth control implant (Implanon/ Nexoplan)	2 ☐	1 ☐	☐☐ years and ☐☐ months
Hormonal IUD (Mirena)	2 ☐	1 ☐	☐☐ years and ☐☐ months

HIV

5. Have you tested positive for HIV since your last screening visit?

- yes	1 ☐	
- no	2 ☐	**Go to question 6**

If yes:

When did you test positive? ☐☐ calendar month ☐☐☐☐ calendar year

When did you have your last CD4 count test?
(If more than 6 months ago → refer the woman for a new test)

☐☐ calendar month ☐☐☐☐ calendar year

What was the result of the CD4 count? _____number

Have you ever been started on ARV treatment?

- yes	1 ☐
- no	2 ☐

If yes:

			started when ?		
First line	1 ☐ Yes	2 ☐ No	**If yes**	☐☐ calendar month	☐☐☐☐ calendar year
Second line	1 ☐ Yes	2 ☐ No	**If yes**	☐☐ calendar month	☐☐☐☐ calendar year
Third line	1 ☐ Yes	2 ☐ No	**If yes**	☐☐ calendar month	☐☐☐☐ calendar year

What is your CTC card number? _____ Clinic name _____ Card number

What is your CTC file number? _____ File number

If you do not know, can we call you and get the number?

- yes	1 ☐
- no	2 ☐

ATTENDANCE TO FOLLOW-UP APPOINTMENT

6. Which of following tools were most important for you to remember your appointment today? *(choose one answer)*

I remembered from my appointment card and came to the clinic	1 ☐	**Go to question 8**
I had a sms-reminder and came to the clinic	2 ☐	**Go to question 8**
A nurse called me and told me to come to the clinic	3 ☐	**Go to question 7**
A nurse visited me at home and told me to come to the clinic	4 ☐	**Go to question 7**
A nurse visited and we had the appointment at my home	5 ☐	**Go to question 7**

7. What are the main reasons why you did not come to the clinic before the nurse contacted you?

I could not afford transportation on my own	Yes 1 ☐	No 2 ☐
I did not think the appointment was important	Yes 1 ☐	No 2 ☐
I had forgotten	Yes 1 ☐	No 2 ☐
I was nervous about the result of the screening	Yes 1 ☐	No 2 ☐
I was nervous about having a gynaecological examination	Yes 1 ☐	No 2 ☐
House chores prevented me from coming	Yes 1 ☐	No 2 ☐
The clinic is too far away from my home	Yes 1 ☐	No 2 ☐
Rainy season/ public holidays	Yes 1 ☐	No 2 ☐
My family does not know that I go, so I have to go secretely	Yes 1 ☐	No 2 ☐
I had my period	Yes 1 ☐	No 2 ☐
I was pregnant	Yes 1 ☐	No 2 ☐
I had moved	Yes 1 ☐	No 2 ☐
Other *(please write)* ……		

HEALTH EDUCATION BY MOBILE PHONE
(ELIMU YA AFIA QUA SIM)

8. Have you received any text messages (sms) regarding cervical cancer and your screening appointment at the clinic?

- yes 1 ☐	
- no 2 ☐	**(Questionnaire is <u>finished</u>)**

<u>If yes:</u>

How do you like the number of messages that you received?

Too many messages	1 ☐
Adequate amount of messages	2 ☐
Too few messages	3 ☐

How do you feel about of the following statements? *(If 'don't know' leave box empty)*

The information in the messages was easy to understand	Yes 1☐	No 2☐
I did *not* need help from others to read the messages	Yes 1☐	No 2☐
The information in messages made me uncomfortable	Yes 1☐	No 2☐
I know how to read text messages on my phone	Yes 1☐	No 2☐
I often send and receive text messages on my phone	Yes 1☐	No 2☐
I shared the health education that I got on my phone with friends or family	Yes 1☐	No 2☐
I would like to continue to receive health information by mobile phone	Yes 1☐	No 2☐
My husband or other family members was happy that I received health information on my mobile phone	Yes 1☐	No 2☐
I would recommend a friend or a family member to receive health education by mobile phone	Yes 1☐	No 2☐

How do you feel about receiving health information and reminders of your appointment via sms on your mobile? *(Choose the one smiley that best shows how you feel)*

Utajisikiaje ukipata ujumbe mfupi wenye taarifa kuhusu saratani ya shingo ya kizazi na upimaji wake kwenye simu yako au? (Chagua tabasamu sahihi kuonyesha utakavyojisikia)


I do not like it at all ☐


I do not like it ☐


It is not okay ☐


It is okay ☐


I like it ☐


I like it very much ☐

Here are some statements about cervical cancer. I will ask you to answer which are true and which are false? *(only for women that have received sms'!)*

Sentensi zifuatazo zinahusu saratani ya shingo ya kizazi. Sema kweli au si kweli kwa kila sentensi

1. Malaria (mbu) inasababisha saratani ya shingo ya kizazi *(Malaria (mosquito) causes cervical cancer)*	Kweli ☐	Si kweli ☐
2. Kupata maumivu wakati wa kukojoa ni dalili ya saratani ya shingo ya kizazi *(Pain during urination can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
3. Saratani ya shingo ya kizazi ndiyo inayoongoza kwa magonjwa ya kanza za wanawake hapa Tanzania *(Cervical cancer is the most commen cancer disease among Tanzanian women)*	Kweli ☐	Si kweli ☐
4. Unaweza kupata saratani ya shingo ya kizazi kwa kubusiana *(You can get cervical cancer from deep kissing)*	Kweli ☐	Si kweli ☐
5. Inawezekana kujikinga na saratani ya shingo ya kizazi *(It is possible to prevent cervical cancer)*	Kweli ☐	Si kweli ☐
6. Kutokwa damu ukeni ni dalili kuu ya ugonjwa wa saratani ya shingo ya kizazi *(Vaginal bleeding is the most common sign of cervical cancer)*	Kweli ☐	Si kweli ☐
7. Jua kali linaweza kusababisha saratani ya shingo ya kizazi *(Too much sun can lead to cervical cancer)*	Kweli ☐	Si kweli ☐
8. Maambukizi ya kwenye shingo ya kizazi mara zote hubadilika kuwa saratani *(A cervical infection will always turn into cancer)*	Kweli ☐	Si kweli ☐
9. Wanawake wenye VVU wako kwenye hatari kubwa ya kupata saratani ya shingo ya kizazi *(HIV-positive women have higher risk of developing cervical cancer)*	Kweli ☐	Si kweli ☐
10. Saratani ya shingo ya kizazi mara nyingi hugundulika mapema kutokana na dalili zake (Cervical cancer is often found at an early stage due to obvious symptoms)	Kweli ☐	Si kweli ☐
11. Unaweza kupata saratani ya shingo ya kizazi kwa kujamiiana bila kinga *(You can get cervical cancer from unprotected sexual intercourse)*	Kweli ☐	Si kweli ☐
12. Kupima afya kunaweza kugundua maambukizi ya kwenye shingo ya kizazi na kuyazuia yasibalike kuwa saratani *(Screening can detect cervical infections so they do not develop into cancer)*	Kweli ☐	Si kweli ☐
13. Saratani ya shingo ya kizazi inaongoza kwa kusababisha vifo vinavyotokana na saratani kwa wanawake hapa Tanzania *(Cervical cancer is the main cause of cancer-related death among Tanzanian women)*	Kweli ☐	Si kweli ☐
14. Saratani ya shingo ya kizazi mara nyingi huwapata wanawake wakiwa kwenye miaka ya ishirini. *(Cervical cancer is most common for women in their 20's)*	Kweli ☐	Si kweli ☐
15. Kuwashwa ukeni kunaweza kuwa ni dalili ya saratani ya shingo ya kizazi *(Itchiness in the vaginal area can be a sign of cervical cancer)*	Kweli ☐	Si kweli ☐
16. Kirusi kinachoitwa Human papilloma virus ndicho kisababishacho saratani ya shingo ya kizazi *(A virus called "Humanpapiloma virus" (HPV) causes cervical cancer)*	Kweli ☐	Si kweli ☐

Thanks a lot for your help

If there are any comments to add, please write them below