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Human papillomavirus testing using existing nucleic acid testing platforms to screen women for cervical cancer: implementation studies from five sub-Saharan African countries

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ABSTRACT

Objectives To demonstrate acceptability and operational feasibility of introducing human papillomavirus (HPV) testing as a principal cervical cancer screening method in public health programmes in sub-Saharan Africa.

Setting 45 primary and secondary health clinics in Malawi, Nigeria, Senegal, Uganda and Zimbabwe.

Participants 15 766 women aged 25–54 years presenting at outpatient departments (Senegal only, general population) or at antiretroviral therapy clinics (all other countries, HIV-positive women only). Eligibility criteria followed national guidelines for cervical cancer screening.

Interventions HPV testing was offered to eligible women as a primary screening for cervical cancer, and HPV-positive women were referred for visual inspection with acetic acid (VIA), and if lesions identified, received treatment or referral.

Primary and secondary outcome measures The primary outcomes were the proportion of HPV-positive women who received results and linked to VIA and the proportion of HPV-positive and VIA-positive women who received treatment.

Results A total of 15 766 women were screened and tested for HPV, among whom 14 564 (92%) had valid results and 4710/14 564 (32%) were HPV positive. 13 837 (95%) of valid results were returned to the clinic and 3376 (72%) of HPV-positive women received results. Of women receiving VIA (n=2735), 715 (26%) were VIA-positive and 622 (87%) received treatment, 75% on the same day as VIA.

Conclusions HPV testing was found to be feasible across the five study countries in a public health setting, although attrition was seen at several key points in the cascade of care, namely results return to women and linkage to VIA. Once women received VIA, if eligible, the availability of on-site cryotherapy and thermal ablation allowed for same-day treatment. With sufficient resources and supportive infrastructure to ensure linkage to treatment, use of HPV testing for cervical cancer screening as recommended by WHO is a promising model in low-income and middle-income countries.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Implementation of human papillomavirus (HPV) screening occurred in public health clinic settings with services provided by the existing clinical staff across five African countries.
⇒ HPV testing used existing transport networks and testing was integrated onto existing centralised and decentralised testing platforms with spare capacity and ability to conduct HPV tests.
⇒ Testing modalities differed across countries with some countries offering only clinician-collected sampling and others offering only self-sampling.
⇒ A disadvantage of an observational study is that it is prone to confounding and cannot be used to demonstrate causality.
⇒ The results may not be generalisable as site selection across the countries were not randomised.

BACKGROUND

Cervical cancer disproportionately affects women in resource-limited settings as oncogenic human papillomavirus (HPV) vaccination rates are lower in low-income and middle-income countries (LMICs) and access to secondary prevention screening is currently limited.[1 2] The majority of all cervical cancer is caused by persistent infection with HPV,[3 4] however given the relatively slow progression from infection to development of cellular abnormalities and cancer, timely diagnosis of infection and treatment of precancerous lesions can effectively prevent the development of cervical cancer and avert mortality.

The WHO has prioritised HPV testing over simpler visual inspection with acetic acid (VIA) for secondary prevention, where resources permit, due to higher test accuracy, longer screening interval and its compatibility with self-collection.[5 6] Also, scale-up of HPV screening is possible on existing large footprints of nucleic acid amplification test (NAAT) platforms in many LMICs.

Women living with HIV (WLHIV) have a higher risk of persistent HPV infection and once infected are at greater risk of progression to cancer,[7 8] therefore timely screening and treatment is of the utmost concern for this population. It has been reported that more than 50% of the WLHIV in sub-Saharan Africa are co-infected with high-risk HPV types, therefore existing HIV care and treatment programmes may serve as a critical service delivery entry point for HPV screening for WLHIV.[9] Furthermore, HPV testing can be integrated on existing HIV and tuberculosis (TB) testing platforms.

Although the accuracy of HPV NAAT screening and the preventive efficacy of treatment of precancerous lesions have been well documented, there is little evidence on how to implement HPV testing and ensure linkage to care for WLHIV accessing routine services in sub-Saharan Africa outside of research study settings. We assessed the feasibility of HPV testing service implementation across five sub-Saharan African countries. The goal of these implementation studies was to describe the service delivery approaches that enable access to integrated HPV testing using existing NAAT platforms and the linkage systems necessary to ensure women diagnosed as HPV-positive receive onward care, in the context of public health programmes in sub-Saharan Africa.

METHODS

Prospective, observational studies were conducted across 45 clinics in five sub-Saharan Africa countries: Malawi, Nigeria, Senegal, Uganda and Zimbabwe. The primary objective of these studies was to determine the operational feasibility and acceptability of HPV testing, with a focus on WLHIV, as a primary cervical cancer screening method, specifically through the following:

1. To describe linkage to VIA and treatment for HPV-positive WLHIV and the feasibility of the full cascade of care—from HPV testing to VIA to treatment—occurring on the same day for HPV-positive WLHIV with small precancerous lesions (ie, eligible for on-site cryotherapy or thermal ablation).
2. To document patient and healthcare worker opinion on HPV screening and treatment programmes across different service delivery models (eg, self-collected vs clinician-collected sampling).

The primary outcomes measured were the proportion of HPV-positive women who received results and linked to VIA and the proportion of HPV-positive women eligible for cryotherapy or thermal ablation with documented treatment. We also examined HPV prevalence and turnaround times. Outcomes for the second objective included acceptability of self-collected sampling and feasibility of HPV testing.

All studies were designed and conducted within routine programmes with the goal of introducing and integrating HPV testing as a new tool for cervical cancer screening on existing NAAT platforms. Implementation methods were country-specific (table 1). Study periods were 7 months on average and ranged from 1 month (Nigeria) to 14 months (Uganda), between September 2019 and April 2021. Target populations for implementation were selected based on the consultation with each country's Ministries of Health. Most of the study countries have a high burden of HIV and as such selected WLHIV as the priority population they wanted to initially focus on. The one exception was Senegal, which has a significantly lower HIV prevalence. Accordingly, their Ministry of Health decided to offer HPV screening to all women accessing services at health facilities, regardless of HIV-status, allowing for broader impact by including the general population. Age inclusion criteria followed country guidelines and ranged from 25 to 54 years.

Countries implemented one or two different testing models. In the hub and spoke model, hub sites provided on-site testing for samples collected at the same clinic on a near-point-of-care (POC) device, namely Cepheid GeneXpert (Cepheid, Sunnyvale, California, USA). In tandem, a new referral system was created for spoke sites, which collected samples on-site and then transported them to a nearby hub site for testing. Alternatively, a centralised model was reflective of on-site sample collection and then transporting those samples through existing referral systems to a centralised laboratory.

Malawi and Senegal implemented the hub and spoke model. Uganda implemented both testing models; seven sites implemented testing at hub sites while the remaining three sites used testing at a centralised laboratory on Hologic Panther (Hologic, Marlborough, Massachusetts, USA). Both Zimbabwe and Nigeria also implemented a centralised model, with Zimbabwe testing on Hologic Panther while Nigeria used Cepheid GeneXpert (table 1).

Health clinics were purposefully selected based on the locations of existing functional GeneXpert devices with available device capacity or an established sample referral system to a central laboratory. These sites were mostly urban with high patient volumes of WLHIV and on-site availability of VIA and treatment of small precancerous lesions. In all study sites, HPV testing was used as a primary screening tool and leveraged VIA (with cervicography in Zimbabwe) as a triage test for women screening HPV-positive, with all VIA-positive women (visible lesions) being treated, except in Senegal. In Senegal, the standard of care for HPV-positive women was visual assessment of the cervix for treatment (VAT), meaning all HPV-positive women were treated, regardless of whether visible lesions were found. In all countries on-site cryotherapy or thermal ablation treatment was to be provided for treatment of small precancerous lesions. Each country also had at least one site that offered Loop Electro Excision Procedure

Table 1 Human papillomavirus testing study designs, by country

	Malawi	Nigeria	Senegal	Uganda	Zimbabwe
Number of clinics	9 (5 hub, 4 spoke)	10	12 (4 hub, 8 spoke)	10	4
Device	Cepheid GeneXpert	Cepheid GeneXpert	Cepheid GeneXpert	Cepheid GeneXpert (hub) Hologic Panther (centralised)	Hologic Panther
Testing model	Hub* and spoke†	Centralised‡	Hub and spoke	Hub and centralised	Centralised
Sample collection method	Self-collected and clinician-collected	Self-collected and clinician-collected	Self-collected and clinician-collected	Self-collection only	Clinician-collected only
Implementation period	November 2019–April 2020	January 2021	September 2020–December 2020	Hub: September 2019–October 2020 Centralised: July 2020–April 2021	July 2020–December 2020
Number of months	6	1	4	Hub: 14 Centralised: 10	6
Semi-qualitative surveys conducted	Yes	No	No	Yes	No
Patient results receipt model	At next ART visit or by phone call or text message§	Direct from laboratory	By appointment or by phone call or text message	At next ART visit or by phone call or text message	At next ART visit or by phone call or text message
Treatment modalities	On-site cryotherapy or thermal ablation; referral for LEEP and suspicious of cancer	On-site thermal ablation; referral for LEEP and suspicious of cancer	On-site thermal ablation; referral for LEEP and suspicious of cancer	On-site cryotherapy or thermal ablation; on-site LEEP in one site, referral in other nine; referral if suspicious of cancer	Cryotherapy or thermal ablation on-site for some; referral for LEEP and suspicious of cancer
Target population	WLHIV aged 25–49 attending ART clinics	WLHIV aged 25–49 attending ART clinics	All women 30–54 years	WLHIV aged 25–49 attending ART clinics	WLHIV aged 30–49 attending ART clinics

*Hub sites are reflective of near-POC testing offered at on-site laboratories located at the same clinic as sample collection.
†Spoke sites are reflective of sample collection occurring at one clinic and then being transported to a hub site for testing with a near-POC device, Cepheid GeneXpert.
‡Centralised sites are reflective of an established major testing laboratory servicing many clinics in the region and/or country, with existing referral systems and high throughput testing capacity.
§Phone call or text message only advised the patient that the result was ready at the clinic.
ART, antiretroviral therapy ; LEEP, Loop Electro Excision Procedure; POC, point-of-care ; WLHIV, women living with HIV .

(LEEP) to treat larger lesions. All women suspected of cancer were to be referred to national cancer institutes for further evaluation and treatment.

Women were primarily recruited from HIV antiretroviral therapy (ART) clinics through health talks that discussed the benefits of cervical cancer screening and HPV testing. All eligible women who provided informed consent were then offered sample collection from clinicians (Zimbabwe; Aptima Cervical Specimen Collection Transport Kit, Hologic, Marlborough, Massachusetts, USA), or were provided self-collected sampling kits (Uganda; Evalyn Brush, Rovers Medical Devices, Oss, Netherlands), or had the option for either sample collection method (Malawi, Nigeria and Senegal; *self*:FLOQSwabs, COPAN, Brescia, Italy; *clinician*:Cervex-Brush Combi, Rovers Medical Devices, Oss, Netherlands).

All sampling and testing procedures followed manufacturer's instructions. Results were returned to patients either by facility ART staff at the next visit, directly from the laboratory, by scheduled appointment or were informed that their result was ready at the clinic via a phone call or text message.

Data were captured at all participating clinics either directly from clinical registers or using study-specific forms, and then entered into a password-protected electronic database. All countries except Senegal aimed to follow-up patients for a minimum of 90 days after sample collection; Senegal followed-up women for 30 days after testing was completed. Due to the COVID-19 restrictions and delays, most countries had to extend both study enrolment and final data collection, allowing up to 180 days of follow-up. All analyses were adjusted according to the actual amount of follow-up time patients received.

Semi-qualitative questionnaires were administered in Malawi and Uganda to both healthcare workers and patients. Questions were asked about the feasibility and acceptability of both HPV testing and self-sampling. Data on the cost of HPV tests and sample collection kits were also collected from each country, sourced from final invoiced supplier purchase orders submitted and processed by UNICEF Supply Division (Copenhagen, Denmark).

Data analysis was mostly descriptive in nature, with categorical variables presented with numerators and percentages and continuous variables presented using medians and IQR. Turnaround time analyses only included 'per protocol', meaning women who received VIA before receiving their HPV results were excluded. Hazard

Ratios and 95% CIs were calculated using maximum likelihood estimation for parametric regression survival-time models to compare time-to-event data. The *streg* command in Stata was used, as the proportional hazards assumption was not met, and accounted for clinic-level clustering using shared frailties and included country as a co-variate. Kaplan-Meier curves were created to visually compare groups. Data analyses were conducted in Stata V.15 (StataCorp, College Station, Texas, USA).

Patient and public involvement

While patients and the public were not involved in the design, implementation or dissemination of this work, the studies were implemented in public health settings meaning the patients were the main beneficiaries of the new services provided. In two countries patients were also asked about their experiences, with their input being used to later inform scale-up.

RESULTS

A total of 15 766 women were screened and tested across the five countries (table 2), with a median of 42 (IQR: 20–83) HPV tests conducted per month, per clinic. Women were evenly distributed across age groups, with an overall median of 38 years (IQR: 33–43). Most women had never been screened previously for cervical cancer, except in Zimbabwe, where 65% of the women had previously received VIA. In Senegal, where all women were eligible, 2% were HIV-positive.

Of the 15 766 women tested for HPV, 14 564 (92%) results were valid and among those with a valid result 4710 (32%) tested HPV-positive (table 3). Among those HPV-positive women, 3376 (72%) received their result. Nine hundred and fifty-seven women were then removed from the denominator as they did not receive their result before receiving VIA, and therefore did not follow the

Table 2 Characteristics of patients receiving human papillomavirus testing by country

	Malawi	Nigeria	Senegal	Uganda	Zimbabwe	Overall
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total cohort	2320	1344	1618	6611	3873	15 766
Age						
25–29 years	381 (16)	174 (13)	0 (0)	1219 (18)	0 (0)	1774 (11)
30–34 years	518 (22)	244 (18)	366 (23)	1418 (21)	753 (19)	3299 (21)
35–39 years	574 (25)	263 (20)	348 (22)	1416 (21)	1030 (27)	3631 (23)
40–44 years	520 (22)	248 (18)	341 (21)	1337 (20)	1014 (26)	3460 (22)
45–49 years	326 (14)	168 (13)	298 (18)	1221 (18)	956 (25)	2969 (19)
50–54 years	0 (0)	0 (0)	252 (16)	0 (0)	0 (0)	252 (2)
Missing	1 (0)	247 (18)	13 (1)	0 (0)	120 (3)	381 (2)
Marital status						
Married	0 (0)	0 (0)	1455 (90)	4100 (62)	0 (0)	5555 (35)
Single	0 (0)	0 (0)	163 (10)	1880 (28)	0 (0)	2043 (13)
Missing	2320 (100)	1344 (100)	0 (0)	631 (10)	3873 (100)	8168 (52)
Previously screened for cervical cancer						
No	0 (0)	1247 (93)	1118 (69)	5897 (89)	1373 (35)	9635 (61)
Yes	0 (0)	4 (0)	500 (31)	714 (11)	2499 (65)	3717 (24)
Missing	2320 (100)	93 (7)	0 (0)	0 (0)	1 (0)	2414 (15)
HIV status						
Positive	2320 (100)	1344 (100)	28 (2)	6611 (100)	3873 (100)	14 176 (90)
Negative	0 (0)	0 (0)	1159 (72)	0 (0)	0 (0)	1159 (7)
Unknown	0 (0)	0 (0)	431 (27)	0 (0)	0 (0)	431 (3)
Sample collection method						
Self	598 (26)	794 (59)	1003 (62)	6611 (100)	0 (0)	9006 (57)
Clinician	1649 (71)	438 (33)	615 (38)	0 (0)	3873 (100)	6575 (42)
Missing	73 (3)	112 (8)	0 (0)	0 (0)	0 (0)	185 (1)
Testing model						
Hub	1939 (84)	0 (0)	1023 (63)	4551 (69)	0 (0)	7513 (48)
Spoke	381 (16)	0 (0)	595 (37)	0 (0)	0 (0)	976 (6)
Centralised	0 (0)	1344 (100)	0 (0)	2060 (31)	3873 (100)	7277 (46)

Table 3 Cascade of care for HPV testing studies, by country

	Malawi		Nigeria		Senegal		Uganda		Zimbabwe		Overall	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Total tested	2320	2320 (100)	1344	1344 (100)	1618	1618 (100)	6611	6611 (100)	3873	3873 (100)	15766	15766 (100)
Test result												
Negative	2320	1246 (54)	1344	875 (65)	1618	1403 (87)	6611	4185 (63)	3873	2145 (55)	15766	9854 (63)
Positive	2320	957 (41)	1344	302 (22)	1618	199 (12)	6611	1827 (28)	3873	1425 (37)	15766	4710 (30)
Subtype: 16	957	245 (26)	302	48 (16)	199	16 (8)	1827	340 (19)	1425		-	4710
Subtype: 18/45	957	193 (20)	302	54 (18)	199	28 (14)	1827	316 (17)	1425		-	4710
Subtype: other high risk	957	733 (77)	302	251 (83)	199	88 (44)	1827	1393 (76)	1425		-	4710
Invalid/error	2320	47 (2)	1344	167 (12)	1618	9 (1)	6611	83 (1)	3873	207 (5)	15766	513 (3)
Missing	2320	70 (3)	1344	0 (0)	1618	7 (0)	6611	516 (8)	3873	96 (2)	15766	689 (4)
Valid test results	2320	2203 (95)	1344	1177 (88)	1618	1602 (99)	6611	6012 (91)	3873	3570 (92)	15766	14564 (92)
HPV positivity	2203	957 (43)	1177	302 (26)	1602	199 (12)	6012	1827 (30)	3570	1425 (40)	14564	4710 (32)
Received results, HPV-negative	1246	614 (49)	875	544 (62)	1403	1159 (83)	4185	2596 (62)	2145	1547 (72)	9854	6460 (66)
Received results, HPV-positive	957	526 (55)	302	269 (89)	199	187 (94)	1827	1224 (67)	1425	1170 (82)	4710	3376 (72)
Linked to VIA/VAT	526	491 (93)	269	210 (78)	187	157 (84)	1224	748 (61)	213*	113 (53)	2419*	1719 (71)
Received VIA/VAT	491	440 (90)	210	210 (100)	157	157 (100)	748	748 (100)		1180†		2735†
VIA/VAT result												
Positive	440	81 (18)	210	104 (50)	157	143 (91)	748	157 (21)	1180	230 (19)	2735	715 (26)
Negative	440	340 (77)	210	106 (50)	157	0 (0)	748	572 (76)	1180	943 (80)	2735	1961 (72)
Suspected of cancer	440	7 (2)	210	0 (0)	157	12 (8)	748	14 (2)	1180	7 (0)	2735	40 (1)
Inconclusive	440	12 (3)	210	0 (0)	157	0 (0)	748	5 (1)	1180	0 (0)	2735	17 (1)
Missing	440	0 (0)	210	0 (0)	157	2 (1)	748	0 (0)	1180	0 (0)	2735	2 (0)
VIA/VAT-positive, treatment and referral												
Received treatment	81	65 (80)	104	104 (100)	143	140 (98)	157	113 (72)	230	200 (87)	715	622 (87)
Thermal ablation	65	65 (100)	104	104 (100)	140	140 (100)	113	83 (73)	200	1 (1)	622	393 (63)
Cryotherapy	65	0 (0)	104	0 (0)	140	0 (0)	113	27 (24)	200	41 (21)	622	68 (11)
LEEP	65	0 (0)	104	0 (0)	140	0 (0)	113	3 (3)	200	158 (79)	622	161 (26)
Referred	81	3 (4)	104	0 (0)	143	0 (0	157	32 (20)	230	23 (10)	715	58 (8)
Other	81	0 (0)	104	0 (0)	143	0 (0)	157	5 (3)	230	0 (0)	715	5 (1)
No documentation	81	13 (16)	104	0 (0)	143	3 (2)	157	6 (4)	230	1 (0)	715	23 (3)
Suspected of cancer, referral												
Referred	7	4 (57)	0	NA	12	0 (0)	14	14 (100)	7	6 (86)	40	24 (60)

Continued

Table 3 Continued

	Malawi		Nigeria		Senegal		Uganda		Zimbabwe		Overall	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Colposcopy	7	0 (0)	0	NA	12	9 (75)	14	0 (0)	7	0 (0)	40	9 (23)
No documentation	7	3 (43)	0	NA	12	3 (25)	14	0 (0)	7	1 (14)	40	7 (18)

*Nine hundred and fifty-seven women were removed from the denominator as they did not receive their result before receiving VIA, and therefore did not follow the cascade of care, of being linked to VIA after receiving their result.
†These 957 women are then added back into the cascade here, as they did receive VIA, along with 110 women who received VIA without ever receiving their HPV results (and the 113 who received results and then VIA).
HPV, human papillomavirus ; LEEP, Loop Electro Excision Procedure; VAT, visual assessment of the cervix for treatment ; VIA, visual inspection with acetic acid.

cascade of care, of being linked to VIA after receiving their result and 2735 received VIA or VAT. A little more than one-quarter of women were VIA-positive (715/2735, 26%); excluding the women from Senegal as all are considered VIA-positive under their screening guidelines, VIA-positivity is reduced to 22% (572/2578). Among the 715 women eligible for treatment, 622 (87%) received treatment.

HPV positivity in WLHIV ranged from 43% in Malawi to 26% in Nigeria. In Senegal, HPV positivity was 26% among HIV-positive women, 11% among HIV-negative women and 15% among women with unknown HIV status. Among HIV-positive women, HPV-positivity decreased with age, with women aged 25–29 years having the highest prevalence at 41% and women aged 45–49 years having the lowest at 31%.

Retention across the cascade of care

Turnaround times (TAT) from sample collection to clinic receipt varied by testing model. For hub sites with near-POC testing, median TAT was 1 day (IQR: 0–3) with 99% of the results being returned to the clinic within 180 days. In comparison, spoke sites had a median TAT of 7 days (IQR: 3–12) with 89% of the results returned within 180 days and sites referring samples to centralised laboratories had a median TAT of 38 days (IQR: 21–48) with 92% results returned within 180 days. Corresponding HRs and 95% CIs with hub sites as the reference were 0.10 (95% CI: 0.02 to 0.60) for spoke sites and 0.14 (95% CI: 0.03 to 0.59) for sites referring to centralised laboratories (figure 1a). Overall, 95% of the results were returned to clinics with a median TAT of 6 days (IQR: 1–35).

The median time from clinic to patient receipt was 6 days (IQR: 0–38) for hub sites with 72% of the results returned to patients within 180 days. In comparison, spoke sites had a median TAT of 5 days (IQR: 1–14) with 63% of the results returned to patients by 180 days, and a median time of 12 days (IQR: 2–52) from clinic to patient receipt for sites referring to centralised laboratories with 67% of the results returned within 180 days. Corresponding HRs and 95% CI with hub sites as the reference were 0.52 (95% CI: 0.22 to 1.16) for spoke sites and 0.56 (95% CI: 0.17 to 1.86) for sites referring to centralised laboratories (figure 1B). Overall, 68% of all patients tested received results, with slightly more HPV-positive women receiving results than HPV-negative women (72% vs 66%, p=0.55).

Among HPV-positive women, the median time from receiving their HPV result to receiving VIA was 0 days (IQR: 0–1) for hub sites, 0 days (IQR: 0–7) for spoke sites and 8 days (IQR: 0–25) for sites referring to centralised laboratories. We did observe women at hub sites were more likely to receive VIA than spoke sites (HR: 0.54, 95% CI: 0.32 to 0.91) and at sites referring to centralised laboratories (HR: 0.41, 95% CI: 0.20 to 0.82) (figure 1C).

Finally, among VIA-positive women we again saw no difference between testing models (figure 1D). The median time from VIA to treatment was 0 days (IQR: 0–0) for all testing models, 87% of VIA-positive women

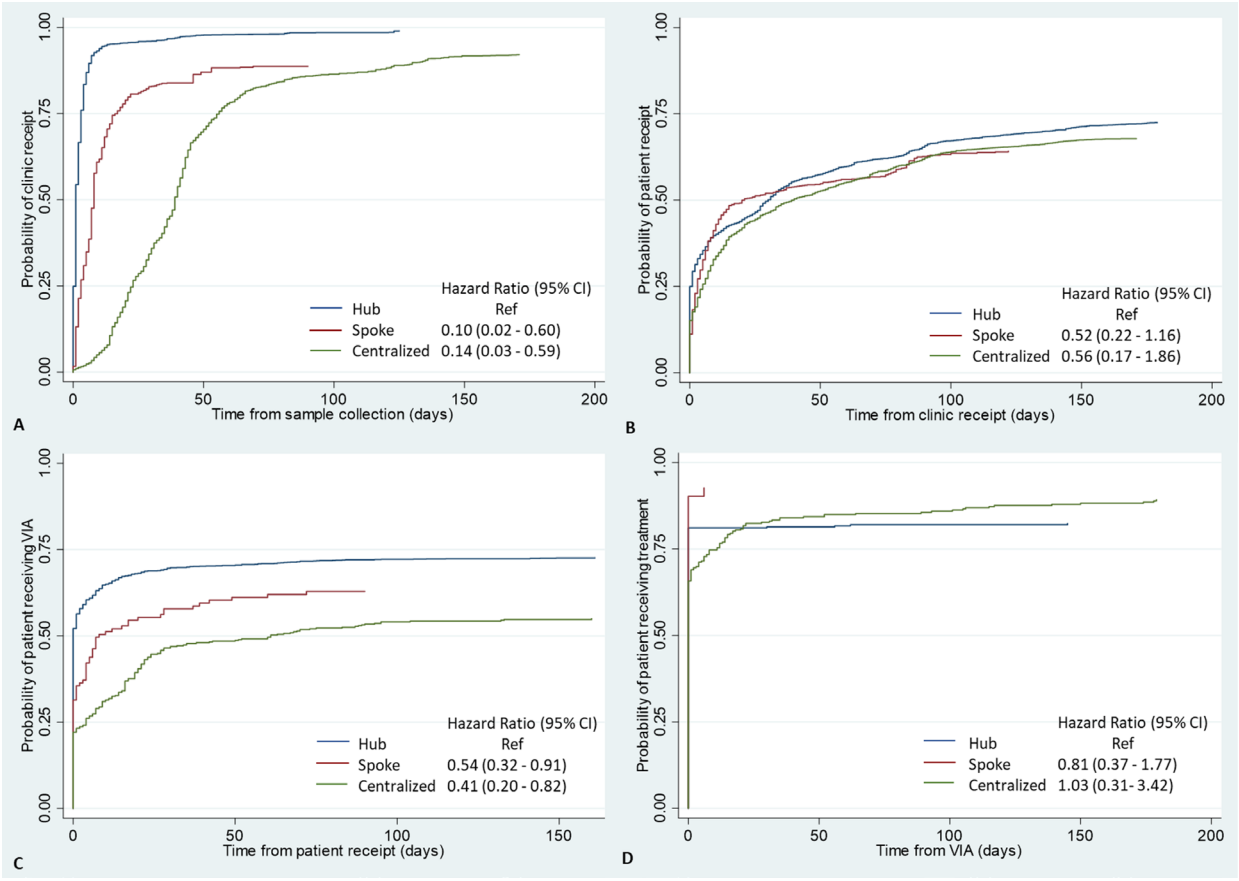

Figure 1 Kaplan-Meier curves showing (A) sample collection to receipt of results at the health clinic; (B) receipt of results at the health clinic to receipt by patient; (C) receipt of result by patient to receipt of VIA (HPV-positive and received result only); (D) receipt of VIA to treatment (VIA-positive only), for HPV testing at hub sites compared with spoke sites and sites referring to centralised laboratories. HPV, human papillomavirus; VIA, visual inspection with acetic acid.

received treatment, with 75% of those needing treatment receiving it on the same day as VIA. For overall TAT between sample collection and treatment, 16% of the patients in hub sites, predominantly in Malawi, were able to be tested and treated on the same day, with all being treated using thermal ablation. By 180 days 82% of the eligible patients had received treatment in hub sites compared with 93% at spoke sites and 87% for sites referring to centralised laboratories.

Including all the women from Zimbabwe who received VIA (whether before or after result was received), a total of 2735 (58%) HPV-positive women received VIA within 180 days, with 715 (26%) VIA-positive, 40 (1%) suspected of cancer and 17 (1%) inconclusive. Eighty-seven per cent of the women eligible for treatment received VIA, ranging from 72% in Uganda to 100% in Nigeria. Across all countries the majority (63%) of the women were treated by thermal ablation and the remaining with either cryotherapy or LEEP; 8% were referred for treatment or services not offered at the clinic. Five (1%) women received other treatment (eg, hysterectomy) and 23 (3%) women had no documentation of treatment or referral. For the 40 women suspected of cancer, 24 (60%) were referred, 9 (23%) women first received a colposcopy and 7 (18%) lacked documentation of the next phase of care.

We did see some differences by country in retention across the cascade of care, with Malawi achieving same-day TAT for their hub sites for both sample collection to clinic (IQR: 0–1) and clinic to patient receipt (IQR: 0–16), but a TAT of 9 days (IQR: 8–15) to clinic receipt of results and an additional 54 days (IQR: 21–83) to patient receipt at spoke sites. Senegal took 2 days (IQR: 1–4) to return results to the clinic and then 0 days (IQR: 0–0) to return results to the patient at hubs sites and 4 days (IQR: 2–8) and 3 days (IQR: 1–7) for results returned to clinic and patient, respectively, for their spoke sites. In Uganda, hub sites took a total of 28 days (IQR: 7–63) from sample collection to return results to the patient but almost double that (58 days, IQR: 30–128) for sites referring to centralised testing. Nigeria's TAT from sample collection to patient receipt of results was 40 days (IQR: 39–41). Zimbabwe took the longest to return results to the patients at 62 days (IQR: 42–92).

Same-day receipt of results at the clinic (hub sites only)

At hub sites where near-POC testing was available, 25% of all results were returned to the clinic on the same day as sample collection. We looked at the impact of same day clinic receipt on HPV-positive and VIA-positive patients receiving treatment. Eighty-four per cent of HPV-positive

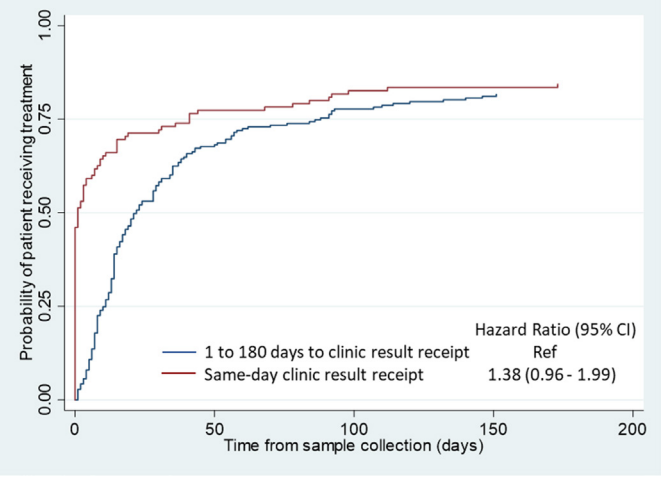

Figure 2 Kaplan-Meier curves of hub sites showing the turnaround time from sample collection to treatment, for HPV-positive and VIA-positive women in clinics receiving results on the same day as sample collection in comparison to clinics receiving results from 1 to 180 days after sample collection. HPV, human papillomavirus; VIA, visual inspection with acetic acid.

and VIA-positive women who had a same day clinic receipt received treatment by 180 days in comparison to 81% of the women whose results were received 1–180 days at the clinic (HR: 1.38, 95% CI: 0.96 to 1.99) (figure 2), showing no statistically significant difference in patient outcome.

Acceptability of self-collected sampling

Overall, 57% of the women provided self-collected samples; in Senegal and Nigeria about 60% of the women self-collected their sample. In Malawi, although only 26% of the women used self-collection kits, 100% of the women surveyed (n=149) on acceptability of self-collected sampling recommended it, with all but two women saying they found the self-sampling procedure easy to perform. Similarly, in Uganda all women recommended self-sampling and all but 7 of the 217 (97%) women surveyed also reported that the self-sampling procedure was easy to perform. In Malawi, where women had a choice between self-collection and clinician-collection, women responded that they chose self-sampling because of its ease, followed by the ability to have privacy.

Feasibility of HPV testing

All healthcare workers surveyed found HPV testing to be feasible and cited that it was easier to perform and more reliable than VIA, as well as improving cervical cancer screening services. They also found most tasks such as documentation of patient information, pre-counselling, preparation and collection of sample materials and post-counselling to be easy. The most difficult task reported by healthcare workers was returning HPV-positive results to patients.

Costing

As a part of the HPV study, countries accessed an average price of US$11.92 for the HPV test alone across all the tests used, with the lowest HPV test cost of US$9.00. When accounting for logistics, distributor margins, controls and other procurement-related costs, the average total cost per test paid was US$13.23 with the lowest total cost paid of US$9.91 per test. Sample collection kits added additional costs to the required procurement including collection media, collection swabs or brushes and ancillary consumables (eg, barcodes, gloves) for adequate sample collection. These collection kits ranged from a low of US$0.50 to US$7.40, depending on the sample collection kit being used. This resulted in an overall lowest total consumable cost for HPV test and sample collection of US$10.41.

DISCUSSION

Introduction of HPV testing in government-run clinics was feasible across all five countries. HPV prevalence among WLHIV was 35%, which is similar to what other studies have found in sub-Saharan African countries when testing for high-risk HPV type.[10–14] Similarly, the 3% invalid rate across all countries appears to be on par with other HPV studies, which reported invalid rates ranging from 1% to >10%.[15 16] Our 3% invalid rate is also similar to the 2% invalid rate we observed in another study that used near-POC devices for early infant diagnosis in an implementation study that had more than 15 000 participants.[17] The one outlier was Nigeria, with an invalid rate of 12%. When investigated, they reported having a high rate of samples collected from actively menstruating women. As their implementation for this pilot was only a month, we did not see an improvement, but the error was addressed with healthcare workers providing additional counselling and we did see improvements later in programmatic data.

Decentralised versus centralised testing models

Hub sites were able to receive HPV test results back at the clinic and subsequently to the patient quicker than either spoke or centralised testing sites. However, this did not translate into significantly higher proportions of women receiving results over the extended 180-day follow-up period across the three testing models. Also, testing models did not appear to impact the TATs or linkage rates from VIA to treatment, as there was no significant difference in the proportion of eligible women that received treatment by 180 days.

Single visit approach

The ideal implementation model for women receiving cervical cancer screening is an approach whereby HPV sample collection, results, triage and treatment would be available in a single visit. Two studies have shown that near-POC HPV testing can achieve same-day results turnaround and treatment, although in both studies it appears that the near-POC devices were dedicated to only HPV testing.[15 18] In contrast, we found that the TAT from sample collection to treatment was rarely same day, even at hub sites (16%), in large part because HPV testing was integrated onto devices that were already being used

for other near-POC tests such as TB diagnosis, HIV early infant diagnosis or HIV viral load, and these tests were usually prioritised over HPV. Consequently, availability of HPV results at the clinic on the same day did not always translate into patient receipt of results in a single visit, as not all women were willing or able to wait for the test results. So, while integration is feasible, in programmatic settings it did not translate into faster diagnoses, as other studies have found.[19] As such, one option can be sample prioritisation, as demonstrated by Malawi, where samples received by 10:00 were prioritised and women would wait to receive their results. If same-day results receipt to the clinic and patient can be ensured, this can lead to VIA and treatment occurring in the same visit, as both can be offered on-site. In the absence of ensuring patient result receipt in a single visit with near-POC devices, a centralised model might prove the most efficient due to economies of scale, although cost and time considerations to the patient must be acknowledged as well as an increased risk of lost to follow-up.

Improving patient results receipt and linkage to care

Only 72% of the patients received their results. The cause of low rate of result return was multifactorial including service disruptions due to COVID-19, transportation costs to return to the facility and staffing bandwidth that limited contact tracing. One major assumption prior to the COVID-19 pandemic was that all women would be returning to the facility on a regular basis. Consequently, a larger factor influencing result return was the fact that women no longer needed to go to the facility to pick up their antiretrovirals (due to newly formed community groups), or because of restricted travel/lockdowns, that prevented women from returning to the health facility in a timely manner. Another factor for low rate of result return was that even when women returned for ART refills, ART staff were not aware that communicating an HPV test result was needed. This was mitigated in Uganda by applying result stickers to patients' files as a reminder to return the results to patients. In Senegal, healthcare workers proactively counselled women on the importance of returning for their results and scheduled appointments for the women to receive results the following day and in Malawi community health workers were used to follow-up with HPV-positive women. All countries provided some degree of proactive outreach to patients through follow-up phone calls as well, but only in Senegal were they fully resourced to do this effectively.

Although linkage rates did vary by country, the overall proportion of HPV-positive women who received their results and then went on for VIA (71%) is very close to a comparable public sector HPV screening and triage programme conducted in three Central American countries.[16] Some reasons for lower linkage proportions include limited human resource capacity at maternal and child health or family planning service points where VIA was offered leading to patient loss due to overcrowding and long lines. Ensuring sufficient on-site capacity for VIA for HPV-positive women is critical to mitigate this loss-to-follow-up.

Finally, the TAT between receiving VIA and treatment was almost always performed on the same day, due to on-site treatments that were available, in particular thermal ablation. Our findings of 75% for same-day VIA to treatment were slightly lower than a recent study conducted in Cameroon that achieved 85%.[20]

Self-collected versus clinician-collected sampling

In Malawi, Senegal and Nigeria the number of samples collected by method (self vs clinician) was driven by the supply purchased, not by demand. Anecdotal information as well as the patient questionnaires confirmed that women were very receptive to self-sampling. In Senegal, most women preferred to have the clinician perform sample collection, due to trusting a health profession and wanting to benefit from their knowledge. The one exception was in the capital city of Dakar, where more women preferred self-collection, probably due to higher education levels. Nigeria also saw a general preference for self-sampling, as it was particularly helpful in addressing some of the known barriers to screening such as privacy concerns, non-attenders, fear of discomfort and convenience.[21] Overall self-collected sampling was found to be feasible, acceptable and may allow for increased testing coverage through implementation of novel screening models both within and outside of a clinical setting.

Costing

The lowest total price we found for combined HPV test and sample collection was US$10.41. This accessible price is significantly lower than many other reported costs in the literature of US$16 or more per test.[22] Pricing is becoming more accessible with overall consumable costs of less than US$10 recently reported in some countries[23] and 2021 published global pricing as low as US$5 per HPV test.[24] While HPV programme costs include reagents, consumables, personnel, trainings and capital costs, recent studies have found that reagent and consumable costs are a major driver of total HIV programme costs, making up more than 60% of the total.[25 26] Leveraging global pricing deals and projected testing demand will allow programmes to minimise these costs.

Strengths and limitations

To our knowledge, this was the first time HPV testing was offered within the public health sector in each of the five countries. Consequently, we could not design a more robust study, as there was no 'pre' implementation period we could compare to, as HPV testing was just being introduced into these facilities, which meant analyses were mostly descriptive in nature. Changes over time were not factored in, and other influences at hand could have affected the outcomes. Another limitation was that we assessed data 180 days after sample collection, but given long delays we know that some women did access care after this time frame, meaning we could be

under-reporting linkage to care and treatment proportions. We could also be under-reporting on the proportion treated, as we did not follow-up on women who were referred, specifically for LEEP. Although efforts were made to ensure data was of high quality in this study, we were limited by what was available in routinely collected registers and patient record data available at health facilities and laboratories. This limitation also meant that we were unable to calculate recruitment rates or uptake of HPV testing. Finally, this study did not look at the comprehensive implementation costs and future research should consider conducting a cost-effectiveness analysis.

Conclusions

HPV testing was successfully implemented for the first time in five public health programmes in sub-Saharan Africa. As previously shown, using high-precision screening in LMICs is possible and will further the fight to eliminate cervical cancer.[16] HPV testing has been shown to increase uptake when paired with self-sampling, provide better performance in terms of testing accuracy and allow for longer screening intervals relative to VIA.[5 27] Our findings demonstrated that offering self-collected sampling and using existing near-POC and centralised devices to integrate HPV testing are both feasible, and although we saw faster results return to patients tested at hub sites using near-POC devices, overall proportions of results received by 180 days did not differ significantly between hub, spoke or centralised testing models. Similarly, we saw no difference in the proportion of women receiving treatment based on the testing model used. We also found that VIA and treatment in a single visit was feasible with the availability of on-site treatment.

Regardless of testing model, we observed a significant drop-off in women receiving HPV results and returning for triage and treatment. Although Malawi was able to see some same-day test and treat results, the other countries that also had near-POC device testing at hub sites—Uganda and Senegal—did not, despite revised laboratory workflows and result return procedures. These challenges highlight the need for sufficient resources and supportive infrastructure to ensure that the test results are returned to women and are linked to VIA and treatment, regardless of testing modality. This can be achieved through proactive and community outreach to patients and reminders in patient files to ensure appropriate clinical action. Furthermore, true-POC solutions coupled with on-site treatment options may allow for a same-day test and treat model. Current programmes should also consider leveraging the HPV systems available in the country, as integration was found to be feasible. Pricing, operational feasibility, available capacity and geographical reach of systems should be considered when selecting models. Overall, we demonstrate HPV testing for cervical cancer screening as recommended by WHO is a promising model in LMICs.

Dissemination to participants and related patient and public communities

Each country has presented their study findings to group key stakeholders and Ministry of Health officials. Global dissemination has included a poster presentation at the 2022 Conference on Retroviruses and Opportunistic Infections. The results will also be disseminated by our company's social media channels and internal and external webinars may be planned.

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Patient consent for publication Not applicable.

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REFERENCES

1 Dorji T, Nopsopon T, Tamang ST, *et al*. Human papillomavirus vaccination uptake in low-and middle-income countries: a meta-analysis. *EClinicalMedicine* 2021;34:100836.
2 Ferlay J, Soerjomataram I, Dikshit R, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–86.
3 Walboomers JM, Jacobs MV, Manos MM, *et al*. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol* 1999;189:12–19.
4 Koshiol J, Lindsay L, Pimenta JM, *et al*. Persistent human papillomavirus infection and cervical neoplasia: a systematic review and meta-analysis. *Am J Epidemiol* 2008;168:123–37.
5 WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. WHO Guidelines Approved by the Guidelines Review Committee. Geneva 2021.
6 WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention: Use of mRNA tests for human papillomavirus (HPV). WHO Guidelines Approved by the Guidelines Review Committee. Geneva 2021.
7 Denslow SA, Rositch AF, Firnhaber C, *et al*. Incidence and progression of cervical lesions in women with HIV: a systematic global review. *Int J STD AIDS* 2014;25:163–77.
8 Liu G, Sharma M, Tan N, *et al*. HIV-positive women have higher risk of human papilloma virus infection, precancerous lesions, and cervical cancer. *AIDS* 2018;32:795–808.
9 Okoye JO, Ofodile CA, Adeleke OK, *et al*. Prevalence of high-risk HPV genotypes in sub-Saharan Africa according to HIV status: a 20-year systematic review. *Epidemiol Health* 2021;43:e2021039.
10 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. *Sex Transm Dis* 2013;40:737–43.
11 Taku O, Businge CB, Mdaka ML, *et al*. Human papillomavirus prevalence and risk factors among HIV-negative and HIV-positive women residing in rural Eastern Cape, South Africa. *Int J Infect Dis* 2020;95:176–82.
12 Baay MFD, Kjetland EF, Ndhlovu PD, *et al*. Human papillomavirus in a rural community in Zimbabwe: the impact of HIV co-infection on HPV genotype distribution. *J Med Virol* 2004;73:481–5.
13 Huchko MJ, Ibrahim S, Blat C, *et al*. Cervical cancer screening through human papillomavirus testing in community health campaigns versus health facilities in rural Western Kenya. *Int J Gynaecol Obstet* 2018;141:63–9.
14 Kelly HA, Chikandiwa A, Sawadogo B, *et al*. Diagnostic accuracy of cervical cancer screening and screening-triage strategies among women living with HIV-1 in Burkina Faso and South Africa: a cohort study. *PLoS Med* 2021;18:e1003528.
15 Kunckler M, Schumacher F, Kenfack B, *et al*. Cervical cancer screening in a low-resource setting: a pilot study on an HPV-based screen-and-treat approach. *Cancer Med* 2017;6:1752–61.
16 Holme F, Jeronimo J, Maldonado F, *et al*. Introduction of HPV testing for cervical cancer screening in Central America: the scale-up project. *Prev Med* 2020;135:106076.
17 Boeke CE, Joseph J, Wang M, *et al*. Point-of-care testing can achieve same-day diagnosis for infants and rapid ART initiation: results from government programmes across six African countries. *J Int AIDS Soc* 2021;24:e25677.
18 Vallely A, Tollman P. Health service delivery models for scaling use of point-of-care HPV 'test and treat' strategies in high-burden, low-income settings. *J Virus Erad* 2019;5:1–3.
19 Wang M, Boeke CE, Rioja MR, *et al*. Feasibility and impact of near-point-of-care integrated tuberculosis/HIV testing in Malawi and Zimbabwe. *AIDS* 2021;35:2531–7.
20 Metaxas T, Kenfack B, Sormani J, *et al*. Acceptability and safety of thermal ablation to prevent cervical cancer in sub-Saharan Africa. *BMC Cancer* 2022;22:132.
21 Nelson EJ, Maynard BR, Loux T, *et al*. The acceptability of self-sampled screening for HPV DNA: a systematic review and meta-analysis. *Sex Transm Infect* 2017;93:56–61.
22 Vodicka EL, Babigumira JB, Mann MR, *et al*. Costs of integrating cervical cancer screening at an HIV clinic in Kenya. *Int J Gynaecol Obstet* 2017;136:220–8.
23 Campos NG, Tsu V, Jeronimo J, *et al*. Cost-effectiveness of an HPV self-collection campaign in Uganda: comparing models for delivery of cervical cancer screening in a low-income setting. *Health Policy Plan* 2017;32:956–68.
24 Diagnostic pricing database, 2021. Available: https://aslm.org/resource/diagnostic-pricing-database/
25 Devine A, Vahanian A, Sawadogo B, *et al*. Costs and cost-effectiveness of cervical cancer screening strategies in women living with HIV in Burkina Faso: the HPV in Africa Research Partnership (HARP) study. *PLoS One* 2021;16:e0248832.
26 Quentin W, Adu-Sarkodie Y, Terris-Prestholt F, *et al*. Costs of cervical cancer screening and treatment using visual inspection with acetic acid (VIA) and cryotherapy in Ghana: the importance of scale. *Trop Med Int Health* 2011;16:379–89.
27 Yeh PT, Kennedy CE, de Vuyst H, *et al*. Self-sampling for human papillomavirus (HPV) testing: a systematic review and meta-analysis. *BMJ Glob Health* 2019;4:e001351.