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SHORT COMMUNICATION

Re-valuation of annual cytology using HPV self-sampling to upgrade prevention (REACH UP): A feasibility study in women living with HIV in the UK

Paola Cicconi[1,2] | **Charlotte Wells**[2] | **Blanka McCarthy**[3] | **Susan Wareing**[3] | **Monique Ingrid Andersson**[3,4] | **Julie Fox**[5] | **Julianne Lwanga**[5] | **Nisha Pal**[6] | **Fiona Burns**[7,8] | **Clare Woodward**[9] | **Ramona Malek**[10] | **Caroline Anne Sabin**[11,12] | **Lucy Dorrell**[1,13]

[1]Nuffield Department of Medicine, University of Oxford, Oxford, UK

[2]Department of Infectious Diseases, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[3]Department of Microbiology, Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[4]Nuffield Division of Clinical Laboratory Science, Radcliffe Department of Medicine, University of Oxford, Oxford, UK

[5]Guy's and St Thomas' NHS Foundation Trust, London, UK

[6]The Garden Clinic, Upton Hospital, Slough, UK

[7]Institute for Global Health University College London, London, UK

[8]Royal Free London NHS Foundation Trust, London, UK

[9]HIV and Genitourinary Medicine, Milton Keynes University Hospital, NHS Foundation Trust, Milton Keynes, UK

[10]Buckinghamshire Healthcare NHS Trust, Amersham, UK

[11]Centre for Clinical Research, Epidemiology, Modelling and Evaluation, Institute for Global Health, UCL, London, UK

[12]National Institute for Health Research (NIHR) Health Protection Research Unit (HPRU) in Blood Borne and Sexually Transmitted Infections at UCL, London, UK

[13]Oxford NIHR Biomedical Research Centre, Oxford, UK

Correspondence
Paola Cicconi, Jenner Vaccine Trials, University of Oxford, Centre for Clinical Vaccinology and Tropical Medicine (CCVTM), Churchill Hospital Old Road, Headington OX3 7LJ, Oxford, UK.
Email: paola.cicconi@ndm.ox.ac.uk

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British HIV Association

Abstract

Introduction: Current UK guidelines for cervical cancer screening are based on the assumption that most women living with HIV (WLWH) are also high-risk (HR) human papillomavirus (HPV)-positive. We aimed to provide data on prevalence of HR-HPV in WLWH in the UK and to assess feasibility and acceptability of HR-HPV self-sampling in this group.

Methods: Women living with HIV attending six HIV services in London/south of England, with no history of cervical cancer, were enrolled. Participants self-collected a vaginal swab for the detection of HR-HPV, completed a survey about sexual/gynaecological history, attitudes towards annual screening and perception of HR-HPV self-sampling, and were asked to have their annual cervical smear.

Results: In all, 67 women were included: 86.5% were of black ethnicity, the median (range) age was 47 (24–60) years, median CD4 T-cell count was 683 cells/μL [interquartile range (IQR): 527–910], and 95.4% had viral load ≤ 50 copies/mL. All performed the vaginal swab. Eighteen (27%) had no cervical smear results; none of these women attended HIV services where this was routinely offered. No cervical samples were positive for HR-HPV. Three-quarters (75.8%) of participants reported adherence to annual screening, with only one woman (1.5%) attending irregularly. On visual analogue scales (from 0 to 100), median (IQR) acceptability and necessity of smear tests were 100 (75–100) and 100 (85–100), respectively.
Conclusions: Our results suggest that the prevalence of HR-HPV in WLWH in the UK may be low. Self-sampling seems to be acceptable, suggesting, if validated, its potential role in supporting less frequent smear testing and improving screening uptake in WLWH.

KEYWORDS
cervical cancer screening, HIV, HR-HPV, self-sampling

INTRODUCTION

Over 99% of cervical cancer is caused by persistent infection with high-risk (HR) types of human papillomavirus (HPV) [1]. Primary HPV screening involves testing the cervical sample for HR-HPV DNA initially, followed by cytology if HR-HPV is detected. This process provides greater protection against cervical carcinomas compared with cytology alone and is cost-effective [2]. For this reason, the UK National Cervical Screening Programme now recommends primary HR-HPV screening at either 3- or 5-year intervals for women aged 25–64 years [3].

According to current British HIV Association (BHIVA) guidelines, women living with HIV (WLWH) should have annual cytology, as this was the standard screening method in place at the time of their writing [4]. The recommendation for annual tests was based on the assumption that WLWH are highly likely to be HR-HPV positive. Although HIV is associated with increased persistence of HPV infection [5], HR-HPV detection is correlated with low CD4 and uncontrolled HIV replication [6]. Therefore, the prevalence of HR-HPV infection in WLWH in settings with widespread antiretroviral therapy use may no longer be sufficiently high to justify annual tests for all WLWH [6–9], and many WLWH may currently be invited for frequent tests unnecessarily. Over the longer term, this could represent an additional barrier to adherence to the screening programme. This should be a cause for concern because adherence to such programmes tends to be low in WLWH and among migrant women in Europe in particular [8–12]. Lack of information and emotional responses to the test are among the most reported barriers to having a smear in the general population [12,13].

We conducted a small-scale study to provide preliminary data on HR-HPV prevalence in WLWH in the UK. We also aimed to investigate awareness of cervical cancer risk and attitudes towards cervical cancer screening recommendations. Finally, we wished to assess the acceptability of HPV self-sampling in this population, given that this provides a means for women to overcome barriers to having a smear and, in some settings, it might prove cost-effective [13–16].

METHODS

The study (NCT04155294) was approved by NHS Research Ethics Committee London Camden and King Cross, UK (19/LO/0842).

Women were recruited at six UK HIV clinics: Oxford University Hospital; Upton Hospital, Slough; Guy's and St Thomas' Hospital, London; Royal Free Hospital, London; Wycombe Hospital; Milton Keynes University Hospital. Inclusion criteria were: diagnosed with HIV for ≥ 6 months, age 25–64 years, no history of CIN 2/3 and/or treatment for cervical dysplasia, annual smear test due, ability to speak and understand English, and ability to provide informed consent.

At baseline, women completed a survey which was returned to study staff in a sealed envelope so as to minimize social desirability bias and to guarantee confidentiality. Questions included: information on HPV vaccination, sexual and gynaecological history, adherence to, acceptability

and awareness of cervical cancer screening ('How necessary are smear tests to you?'), and attitudes towards self-sampling. Questions were mostly closed, with ordered response choices and with visual analogue scales (from 0 to 100) for the assessment of acceptability and necessity of smear tests. Demographic and clinical data were collected from clinical notes.

Women were also asked to perform a vaginal swab for the detection of HR-HPV after receiving instruction by the study team. They had the option to obtain the sample at home and post it to the laboratory using an addressed pre-stamped envelope. This was the recommended method if they had sexual intercourse within 48 h of the collection to avoid contamination. Women were asked to attend their annual cervical smear and results were accessible to the study team via NHS records. Cervical samples were routinely analysed for HR-HPV, followed by cytology in cases where HR-HPV was detected, in accordance with national guidelines. Date of enrolment was the date of entry questionnaire completion, HR-HPV swab, or smear test, whichever occurred first within a 60-day window.

An exit questionnaire, the vaginal swab and the smear test were repeated after 1 year (data not presented here).

Swabs were analysed at the Department of Microbiology, Oxford University Hospital using the Abbott RealTi*me* High-Risk HPV Test kit [17]. The assay identifies 14 HR-HPV genotypes: 16, 18 and others (31/33/35/39/45/51/52/56/58/59/66/68). Specimens were collected in Hologic ThinPrep solution (Hologic Inc., Marlborough, MA, USA), shipped at room temperature and stored on site at 2–8°C.

Descriptive statistics for all survey questions are presented. The sample size reflected a compromise between feasibility and a reasonably precise estimate of the HR-HPV prevalence (number of positive cervical smears at each time point divided by the number of samples tested).

RESULTS

Sixty-seven of the 77 women enrolled between October 2019 and March 2020 had demographic data available and were included in analyses. The majority (86.5%) were black (African, Caribbean or British) and median age was 47 years [interquartile range (IQR): 24–60]. Their median CD4 count was 683 cells/μL (IQR: 527–910). The majority (95.4%) had HIV viral load < 50 copies/mL (Table 1).

Sixty-six baseline questionnaires were included in the analysis; one questionnaire was not returned. All women except one had had at least one smear test in their life, and 30 (45.5%) had at least one colposcopy. Median (IQR) acceptability and perceived necessity of smear tests were 100 (75–100) and 100 (85–100), respectively. More than half of the women (56.1%) reported no concerns about self-taken swabs; however, one-third reported fear of not doing it properly or having inadequate results. Of note, 75.8% reported adherence to the annual cervical cancer screening, and only one reported doing smears at irregular intervals (Table 2).

TABLE 1 Demographic characteristics of participants

		n
Number of women		67 (100.0)
Enrolment date		21 October 2019 to 6 March 2020
Age (years)	Median (range)	47 (24.60)
Ethnicity	White	6 (8.9)
	Black	58 (86.6)
	Mixed	3 (4.5)
Time since HIV diagnosis (years)	Median (range)	13 (1.29)
Duration of ART (years)	Median (range)	10 (1.23)
Receipt of concomitant medications		44 (65.6)
Nadir CD4 T-cell count (cells/μL) ($n = 54$)	Median (IQR)	247 (117–410)
Current CD4 T-cell count (cells/μL) ($n = 65$)	Median (IQR)	683 (527–910)
Current viral load, $n = 65$	Undetectable	58 (89.2)
	Detectable, ≤50 copies/mL	4 (6.2)
	Detectable, > 50 copies/mL	3 (4.6)

Abbreviations: ART, antiretroviral therapy; IQR, interquartile range.

TABLE 2 Summary results from entry survey

		n
Number of women		66 (100.0)
Number of partners	None	2 (3.0)
	1–5	38 (57.6)
	6–9	7 (10.6)
	10 or more	9 (13.6)
	Not stated	10 (15.2)
Number of partners in last 6 months	0	15 (22.7)
	1	39 (59.1)
	> 1	2 (3.0)
	Not stated	10 (15.2)
Number of pregnancies	Median (IQR)	3 (0–9)
Contraception	No – sterilized	2 (3.0)
	No	46 (69.7)
	Yes	14 (21.2)
	Not stated	4 (6.0)
Smoker	No	56 (84.9)
	Yes	5 (7.6)
	Not stated	5 (7.6)
Ever smoked	No	46 (69.7)
	Yes	15 (22.7)
	Not stated	5 (7.6)
Had HPV vaccine	No	60 (90.9)
	Yes	4 (6.1)
	Not stated	2 (3.0)
Frequency of condom use in last 6 months	Sometimes	10 (15.2)
	Often	3 (4.6)
	Always	15 (22.7)
	Do not use	34 (51.5)
	Not stated	4 (6.1)
Last menstrual period	< 4 weeks	30 (45.5)
	4 weeks–3 months	7 (10.6)
	3–12 months	3 (4.6)
	> 12 months	23 (34.9)
	Not stated	3 (4.6)
Ever had a colposcopy	No	26 (39.4)
	Yes	30 (45.5)
	Do not know	7 (10.6)
	Not stated	3 (4.6)
Ever had a smear	No	1 (1.5)
	Yes	61 (92.4)
	Not stated	4 (6.1)
How often have smears	Annually	50 (75.8)
	2- to 5-yearly	13 (19.7)
	Not regularly	1 (1.5)
	Not stated	2 (3.0)
Acceptability of smear tests ($n = 63$)	Median (IQR)	100 (75–100)
Necessity of smear tests ($n = 63$)	Median (IQR)	100 (98–100)
How painful are smears ($n = 61$)	Median (IQR)	50 (20–70)
Views on swab	No concerns	37 (56.1)
	May not do properly	14 (21.2)
	May be painful	2 (3.0)
	Result not clear	8 (12.1)
	Not answered	8 (12.1)

Abbreviations: HPV, human papillomavirus; IQR, interquartile range.

All women undertook the vaginal swab themselves; three (4.4%) did not perform the swab in the clinic and posted it subsequently (all the posted swabs reached the laboratory). Three swabs did not reach the laboratory for analysis, two leaked during shipment and could not be analysed, and three produced indeterminate results. Of the 59 (88%) swabs analysed successfully, two (3.3%) were positive for HPV18, two (3.3%) were positive for other HR-HPV and for HPV16, and 15 (25.4%) were positive for other HR-HPV.

Eighteen (27%) of the smear test results were not available from their NHS records, suggesting that a significant number of women self-administered the vaginal swab at the study visit but did not attend for their annual smear test. Three sites did not offer the cervical smear routinely, and they recruited a total of 48 women. All 18 women with no smear test results were recruited at these sites; this translates into 63% (30/48) of screening uptake in women who were offered the test outside of the HIV service. By contrast, the screening uptake was 100% (19/19) in women recruited at the study sites where the smear was offered. No other differences emerged between those with and without the cervical smear.

None of the 49 smear samples analysed as part of the National Screening Programme was positive for HR-HPV.

However, HR-HPV was detected in 14/49 (30%) vaginal swab samples. In other words, only in 59.1% of the cases was there concordance between the two tests (i.e both were negative). In addition, five women with missing smear results had positive HR-HPV on the self-administered swabs.

DISCUSSION

In our cohort of WLWH with preserved immune function who were largely unvaccinated against HPV, no HR-HPV was detected in cervical samples. For this reason, and given the small sample size, a formal calculation of HR-HPV prevalence would be inappropriate. HR-HPV prevalence declines with increasing age after 30 years [20], and this could explain the low prevalence we found in our population of older women. Of note, approximately half of our cohort reported having had at least one colposcopy, suggesting that they have had significantly abnormal smears in the past. These data support our initial hypothesis that where antiretroviral treatment is widely available, WLWH tend to clear the HR-HPV infection. For this reason, the assumption that the majority of WLWH are persistently HR-HPV-infected does not hold true, arguing for updated guidelines for cervical screening in this population.

In general, the study showed that self-sampling is feasible in WLWH with no major barriers to recruitment emerging. No women who completed the self-sampling reported side-effects, suggesting few major barriers to its implementation. However, one-third had concerns about the reliability of the results. Confidence in self-sampling can be increased by offering counselling and providing educational material with a description of the procedure.

Our cohort reported high levels of acceptability and awareness of the need for repeated smear tests as a means to determine whether they were at risk of cervical cancer. However, 18 smear test results were not available, showing that one-quarter of our population failed to attend their annual smear. This result confirms the information of our entry survey, where only 75% reported adherence to the screening programme. This percentage is in line with the national uptake of cervical screening in England [18], suggesting that in our population, HIV infection does not seem to represent an additional barrier for adherence to the programme. However, the uptake remains below the NHS target of 80%, and interventions to improve adherence are urgently needed. These should prioritize WLWH attending HIV services where the cervical smear is not routinely offered and the screening uptake seems to be particularly low. Self-sampling integrated in the screening programme and offered annually in the HIV clinic could help to identify the poorly compliant population at higher risk of cervical dysplasia.

A concordant negative result between smears and swabs was obtained from less than two-thirds of women studied. The reason for the discrepancy is unclear and deserves further investigation. The platform used to detect HR-HPV on swabs is approved by the UK Health Security Agency (UKHSA) for HR-HPV detection on cervical samples. One reason why we had such a high proportion of positive results could be contamination of vaginal samples with partners' HR-HPV. Recruitment from the clinic occurred without prior notice, and despite the recommendation of delaying the collection in case of recent sexual intercourse, the majority of women took the test while in the clinic. More than half of our cohort was sexually active, but only 22.7% reported consistent condom use, suggesting that cross-contamination cannot be excluded.

If validation studies confirm that self-sampling for HR-HPV detection is at least as sensitive as the use of cervical samples, there may be a potential role for this method in allowing for longer intervals between smear tests, in at least a group of WLWH with preserved immune function. One possible scenario could see WLWH aligned to the general population for frequency of smear tests, with annual self-sampling. Only those with HR-HPV detected on the swab would require an earlier repeat smear test.

The COVID-19 pandemic has necessitated implementation of remote consultations for non-urgent care. In such circumstances, self-sampling for HPV could ensure women are not lost from surveillance.

We wish to emphasize that validation of HPV self-sampling was not one of our objectives and the study was not powered to make this comparison, limiting conclusions that can be drawn. An ongoing large study from the UKHSA aims to address this question in the general population [19]. Another limitation of our study was the lack of information on 10 women who provided the self-administered vaginal swab in the clinic. The excluded participants were enrolled across all the sites and their exclusion is unlikely to have had a major impact on our findings. The characteristics of the population were homogeneous within and between sites. None of the excluded women had positive smear tests.

CONCLUSIONS

Our results suggest that the prevalence of HR-HPV in the UK population of WLWH is relatively low. Self-sampling for HR-HPV is acceptable and may support less frequent smear testing in this population. At the same time, it may provide a means to identify women at higher risk of cervical dysplasia who do not attend for annual smear tests but who

regularly attend HIV follow-up appointments. However, further validation of the whole testing pathway is required.

Our data provide a foundation to investigate further the potential role of implementing integrated self-sampling HR-HPV primary testing in WLWH and to assess its cost-effectiveness. This in turn will contribute to the current evidence base to modify cervical screening guidance in WLWH.

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AUTHOR CONTRIBUTIONS

Paola Cicconi and Lucy Dorrell contributed to the protocol and design of the study and PC is chief investigator. Charlotte Wells, Blanka McCarthy, Susan Wareing, Monique Ingrid Andersson, Julianne Lwanga, Julie Fox, Nisha Pal, Fiona Burns, Clare Woodward, Ramona Malek, contributed to implementation of the study and/or laboratory experimentation.Caroline Anne Sabin did the statistical analysis. All authors critically reviewed and approved the final version.

ORCID

Paola Cicconi https://orcid.org/0000-0001-6347-966X
Caroline Anne Sabin https://orcid.org/0000-0001-5173-2760

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