



Evaluation and impact of screening and treatment approaches for the prevention of cervical neoplasia in HIV-positive women in Burkina Faso and South Africa

EC Grant Agreement Number: 265396

Final publishable summary report

Author	Philippe Mayaud/Helen Kelly
Submission Date	23 December 2014
Reporting period	1 st November 2010 to 31 st October 2014
Document version	0.1

Table of Contents

A. EXECUTIVE SUMMARY	3
B. PROJECT CONTEXT AND MAIN OBJECTIVES	4
B1. Study 1	4
B2. Study 2	4
B3. Study 3	5
B4. Methodology overview	5
C. MAIN SCIENCE & TECHNICAL RESULTS / FOREGROUNDS.....	6
C1. Prevalence and determinants of cervical lesions and high-risk (hr)HPV infection in HIV-positive African women.....	6
C2. Incidence, persistence and recurrence of CIN2+ and incidence, persistence and clearance of hrHPV at 16 months.....	6
C3. Performance of screening tests for cervical lesions (CIN2+ and CIN3+) in HIV-positive African women	7
C4. Economic evaluation of cervical cancer screening among HIV-positive African women	8
C5. Accuracy of HPV DNA qualitative testing (Digene HC2 and <i>careHPV</i>) vs. genotyping to detect high-risk HPV genotypes and cervical lesions in HIV-positive African women	8
C6. In conclusion	9
C7. Other lessons learned	10
D. POTENTIAL IMPACT, DISSEMINATION ACTIVITIES AND THE EXPLOITATION OF RESULTS	11
D1. Strategic impact.....	11
D2. The use and dissemination of foreground.....	12
D3. Management of intellectual property.....	12
D4. Project website	13
E. HARP CONTACT DETAILS.....	14

A. EXECUTIVE SUMMARY

The rapid extension of antiretroviral therapy (ART) programmes for the treatment of HIV/AIDS across sub-Saharan Africa affords the opportunity to integrate a range of sexual and reproductive health services and interventions and to assess their performance and impact on the morbidity, mortality and quality of life of HIV-positive individuals. Reciprocally, the frequent and intensive follow-up of patients at HIV clinics provides an opportunity to study the effects of HIV-related factors and ART on outcomes, such as cervical neoplasia, in these populations. Prevention of cervical cancer should rank high as a public health priority in sub-Saharan Africa since HIV-infected women represent a group at very high-risk of cervical intraepithelial neoplasia (CIN). However, there are few functional screening programmes across the continent and in particular there are currently no definitive guidelines on how best to manage women living with HIV (WHIV). The hypothesis behind this study was that the use of simple tests able to detect high-risk (HR) HPV genotypes, such as the *CareHPV* test, which has never been evaluated in Africa, alone or combination with other tests in various triage strategies could improve the coverage of cervical cancer screening in these populations and could represent a cost-effective cervical cancer prevention intervention. The inclusion of West and South African cohorts allowed for broader African regional relevance. Cohorts of 624 WHIV in Ouagadougou, Burkina Faso and 625 in Johannesburg, South Africa were recruited from HIV care centres and followed-up over 16 months for:

- (1) The measurement of CIN and hrHPV prevalence, incidence, persistence and clearance, including following treatment; and
- (2) The evaluation of the performance of various screening tests and triage strategies. Economic analyses were performed to allow the development and validation of screening algorithms using locally relevant epidemiological and economic data rarely available from Africa.

The main study findings were:

- (1) The risks for cervical cancer in WLHIV are very high (5% in BF, 22% in SA), although prevalence varies by country and by CD4 count. Being on ART alone does not reduce the risk of hrHPV or CIN2+, but duration of ART, high CD4 and virological control can help decrease risk, highlighting the importance of good and sustained virological control and immune restoration provided by ART to control hrHPV natural history;
- (2) The prevalence of hrHPV is also very high (59% and 79%). Over 80% of cervical lesions identified could be prevented with the next generation HPV vaccine which targets 7 hrHPV;
- (3) In South Africa, the current recommended screening test (cytology with high grade cut off) appears to perform reasonably well, while in Burkina Faso, the addition of HPV test would appear beneficial. Screening tests are most sensitive among women with CD4+ count below 200 cells/ μ L, and screening strategies may need to be further modified according to CD4+ count;
- (4) Compared with genotyping, both qualitative HPV DNA tests (Digene HC2 and *careHPV*) appear equivalently suitable because of their high specificity for specificity for detecting CIN2+ or CIN3+. The negative predictive values of the two tests are similar in performance; and
- (5) The most cost-effective cervical cancer screening strategy for women attending HIV clinics will vary by setting. Programs may want to consider targeting women with lower CD4 counts due to higher CIN-2+ prevalence. Depending on the setting, *careHPV* will not be a cost-effective option unless the price of test components are reduced or donated.

B. PROJECT CONTEXT AND MAIN OBJECTIVES

The overall **aim** of the HARP study was to improve cervical cancer prevention programmes for HIV–infected women in Africa, by evaluating the effectiveness and cost-effectiveness of alternative screening strategies, and by developing algorithms leading to earlier detection and management of cervical cancer in these high-risk populations.

The research programme was comprised of three interlinked studies. **Study 1** was a cross-sectional study of HPV and cervical neoplasia screening among women attending HIV care centres. **Study 2** was a prospective follow-up study of a cohort of women recruited in Study 1 (who did not need to be immediately treated for CIN) for a duration of 18 months in order to evaluate the performance of tests to predict the development of cervical neoplasia. **Study 3** was a modelling study using data from the first two epidemiological studies to determine cost-effectiveness of the various screening strategies.

The specific **objectives** of this research were:

B1. Study 1

To determine, among HIV-infected African women attending HIV care settings:

- 1) the relative diagnostic performance of a novel HR-HPV DNA rapid test (*CareHPV*) vs. other screening tests (cytology, VIA/VILI) to detect high-grade cervical intraepithelial neoplasia (CIN2+). A secondary analysis will evaluate the impact on CIN3+;
- 2) the prevalence of cervical HPV infection, genotype distribution and associations with cytological and histological cervical lesions, according to HIV-related factors (plasma viral load, CD4+ counts) and exposure to combined antiretroviral therapy (ART); and
- 3) the diagnostic accuracy of *CareHPV* to detect specific hrHPV genotypes (demonstrated by HPV genotyping).

B2. Study 2

To determine, among HIV-infected African women without advanced histological lesions (i.e. <CIN2):

- 1) The incidence of histological lesions (CIN2+), and the effects of HIV-related factors (plasma viral load, CD4+ counts) and concomitant exposure to HAART on these at 18 months;
- 2) The clinical relevance of persistent *CareHPV* positivity (at enrolment then at 12 and 18 months) to predict incident CIN2+ at M18. A secondary analysis will evaluate the impact on CIN3+; and
- 3) The incidence, persistence, and clearance of type-specific HPV infection over 18 months and the effects of HIV-related factors (plasma viral load, CD4+ counts) and concomitant exposure to HAART on these outcomes.

To determine, among HIV-infected African women treated for histological lesions (CIN2+):

- 4) The recurrence of CIN2+ lesions at 18 months and their predicting factors.

B3. Study 3

- 1) To model detection rates of CIN2+ using data obtained from Studies 1 and 2 of using alternative combinations of screening tests and screening pathways based on women's characteristics and HIV-related factors and exposure to ART;
- 2) To collect detailed estimates of the incremental costs of implementing cervical cancer screening within existing HIV treatment centres in Africa; and
- 3) To combine these estimates with data from the epidemiological data to estimate the overall cost-effectiveness of alternative strategies in terms of cost-per-case detected.

Information collected from the above studies was intended to enable development of guidelines regarding the best low-cost screening strategies for cervical cancer screening among HIV-infected women in Burkina Faso and South Africa.

In addition, the collected samples were stored to form a repository which can be used for further testing of future alternative tests to detect hrHPV infection, mRNA integration, DNA methylation and other STI/HIV markers. Ethical clearance and participant's informed consent were sought separately for further use of stored samples.

B4. Methodology overview

Eligible and consenting women, were enrolled in a baseline assessment of CIN and various screening assays. In short, participants provided cervical swabs for HPV-DNA testing, using genotyping (INNOLiPA assay, based on SPF10+ primer set eliciting the presence of 28 HPV genotypes including 15 hrHPV), and a qualitative HPV DNA test (Digene HC2 at enrolment, *CareHPV* at 12 months and 16 months), cervical smear for cytology testing (papanicolaou stain), visual inspection with acetic acid/lugol's iodine (VIA/VILI), and a colposcopically directed cervical four-quadrant biopsy which constituted the final diagnosis, if the woman had any abnormal findings on any of the screening assays or during colposcopy. HIV-related parameters (CD4 T-lymphocyte count, HIV-1 RNA plasma viral load, ART status and regimen) were recorded, and testing was performed to detect cervico-vaginal STI (*Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Trichomonas vaginalis*) by PCR, assess vaginal flora by smear microscopy and serological STIs (syphilis and herpes simplex virus type 2 [HSV-2]).

Women found to have CIN2+ at enrolment were offered treatment according to local standards and through local services, usually LEEP excision or cone biopsy.

Participants who did not require hysterectomy were enrolled in a prospective evaluation of CIN and hrHPV over 16 months with assessments for HIV parameters at three time points (months 6, 12 and 16), evaluation of HPV at months 12 and 16), and full evaluation of screening tests and CIN at month 16 to determine CIN incidence and recurrence (following treatment) and hrHPV incidence, persistence or clearance. The role and cost of HPV testing and cytology as possible tests of cure following treatment were also determined.

C. MAIN SCIENCE & TECHNICAL RESULTS / FOREGROUNDS

The main outcomes and results of this study are the following:

C1. Prevalence and determinants of cervical lesions and high-risk (hr)HPV infection in HIV-positive African women

The study enrolled **1249** women living with HIV-1 aged 25-50 years between December 2011 and October 2012 (**625** in Burkina Faso [BF] and **624** in South Africa [SA]). Enrolment was stratified in a pre-specified 2:1 ratio by ART status, with 431 (69.0%) participants on ART in BF and 406 (65.1%) in SA. The median duration on ART at enrolment was 17 months (interquartile range [IQR], 0-64) in BF and 28 months (IQR, 10-50) in SA. In BF, the median CD4+ count was 414 (IQR, 315-606) cells/mm³ among non-ART users and 446 (IQR, 309-600) cells/mm³ among ART users; and in SA, these were 450 (IQR 353-616) cells/mm³ among non-ART users and 420 (IQR 279-569) cells/mm³ among ART users. In SA, the prevalence of classical risk factors for hrHPV and CIN including smoking, hormonal contraception and number of lifetime sexual partners was higher, as well as the prevalence of other STI.

In terms of previous exposure to cervical cancer screening according to local guidelines, nearly a quarter (22%) of participants in BF reported having had a previous visual inspection with VIA, and 50% of SA participants had ever had a pap smear, but only a tiny fraction of participants reported having been treated for cervical abnormality (1.6% in BF and 0.2% in SA). Even though 85% of women had previously heard of cervical cancer, only 14% had ever heard of HPV. 40% had ever been screened for HPV/cervical cancer lesions.

At enrolment, the prevalence of CIN2+ and hrHPV were high in both countries, but much higher in SA. The prevalence of **CIN2+** was **5.7%** in BF and **22.4%** in SA (N=160 CIN2+ cases in all) and hrHPV was **59.6%** in BF and **78.9%** in SA. The HPV genotype distribution was not very dissimilar at both sites, with the most prevalent type being HPV52 (20.2% in BF and 24.1% in SA). HPV33 was most strongly associated with CIN2+ (adjusted odds ratio [OR]=4.33, 95% CI 2.27-8.27). The prevalence of HPV16/18 included in bi and quadrivalent HPV vaccines was only 22%, whilst that of the 7 hrHPV types (16, 18, 31, 33, 45, 52, 58) included in the nonavalent vaccine was 55%, and increased with histological severity of diagnosis: overall, **39%** of prevalent CIN2+ were associated with **HPV16/18** and **84%** were associated with the **7 hrHPV types**.

Both CIN2+ and hrHPV were more prevalent among women with low CD4 ≤ 200 cells/mm³ compared with CD4 ≥ 500 cells/mm³ (CIN2+: adjusted OR=2.49, 95% CI 1.30-4.79; hrHPV: adjusted prevalence ratio [PR] =1.25, 95% CI 1.10-1.43). Being on ART did not in itself reduce the risk of CIN2+ or hrHPV, **but shorter duration of ART, lower CD4 and lack of virological control were all associated with an increased risk**. For example, CIN2+ and hrHPV were more prevalent among those with short duration of ART use (≤ 24 months) compared with those taking ART for ≥ 24 months (CIN2+: adjusted OR=1.80, 95% CI 1.03-3.14; hrHPV: adjusted PR=1.12, 95% CI 1.01-1.23).

C2. Incidence, persistence and recurrence of CIN2+ and incidence, persistence and clearance of hrHPV at 16 months

Overall, **1107 (89%)** participants were followed up for a median duration of 16 months (IQR, 14-17 months). By then, only an additional 4% of participants not yet on ART had been initiated on ART. We recorded 15 deaths overall (1.2%), 9 in BF (1.4%) and 6 (1.0%) in SA.

The 16-month **incidence of CIN2+** was **1.4%** in BF and **4.4%** in SA (N=34 CIN2+ cases in total). **Recurrence of CIN2+** following treatment was around what was anticipated at **8%**, and did not differ by treatment method (mostly LEEP though). There was a high incidence/type swap (32-36%) and persistence (30-35%) of hrHPV among these participants over 16 months, and this was quite similar in both countries. CD4 count, virological control and ART status at enrolment were important factors for persistence and clearance. CIN2+ incidence was strongly linked to hrHPV persistence, mostly due to HPV types 58, 35, 18 and 16 (>50% of all CIN2+).

Over a third (37%) of incident/type swaps hrHPV at 16 months were attributed to one of the 7 hrHPV genotypes (16, 18, 31, 33, 45, 52, 58, in addition to low-risk types 6 and 11) targeted by the recently developed nonavalent vaccine, and none of the participants were infected by all hrHPV genotypes. Two thirds (**63%**) of **incident CIN2+** were associated with infection by any of the **7 genotypes** included in the nonavalent HPV vaccine, but only **40%** with the **classical HPV16/18** targeted by current bi and quadrivalent vaccines. These data indicated:

- 1) the importance of targeting all these types to prevent CIN2+,
- 2) the remaining high-risk of exposure to hrHPV in this population; and
- 3) the potential scope for possible primary prevention of HPV and CIN2+ through vaccination.

Preliminary analyses of hrHPV natural history over 16 months indicate that virological control and immune restoration are important to control hrHPV but this takes time. The project will generate genotype specific insights of the natural history of hrHPV infection.

C3. Performance of screening tests for cervical lesions (CIN2+ and CIN3+) in HIV-positive African women

For the detection of CIN2+ in South Africa, the “best test” is not quite clear. Cytology using high-grade lesions (HSIL or greater, >HSIL) as a cut-off has a relatively low sensitivity (68.9%). Cytology using LSIL and greater (>LSIL) (current guidelines for HIV-negative populations) has high sensitivity (97.6%) but very low specificity (12.5%) resulting in nearly 90% of the population being referred for colposcopy. Adding HPV testing to triage low-grade cytology would lead to reduce the sensitivity (85.7%) (missing a further 15 cases), but improved specificity (54%) reduced the number of confirmatory colposcopies by 39%.

In Burkina Faso, HPV testing was by far the most sensitive test (96.9%) but had the lowest specificity (61.2%). Cytology using low-grade SIL as cut-off performed well (sensitivity 73.3%, specificity 80.3%) but it has to be stressed that this would be under optimal conditions of well quality controlled testing at one of the best centres in the country. Adding HPV testing to cytology marginally lowered the sensitivity (70.0%) but decreased the number of colposcopies by 31%. Visual inspection (current standard of screening) with or without the addition of HPV testing had low sensitivity (56.3%).

For CIN3+ detection in South Africa, cytology with HSIL was the best single test detecting 81% (42/52) of the CIN3+ cases in our study population, yet leading to a low number of colposcopies required, i.e. 4 colposcopies per case detected. Adding HPV triage to cytology reduced the number of colposcopies by 12% but missed a further 4 cases, and reducing the sensitivity to 73.1%.

In Burkina Faso, visual inspection with VIA/VILI detected 11/13 (sensitivity=84.6%) of the CIN3+ cases, however requires 12 colposcopies per case detected. Adding HPV triaging did not alter the sensitivity but reduced the number of colposcopies by 44%, requiring only 7

colposcopies per case detected. HPV testing alone detected all 13 CIN3+ cases (sensitivity=100%) but the specificity was low (59.2%) meaning that of the test combinations, this was the one which required the most colposcopies.

C4. Economic evaluation of cervical cancer screening among HIV-positive African women

The economic analysis combined the inclusion of empirical costs obtained under local operation of the different tests with the epidemiological data on performance of the tests described above, excluding research costs. The results were modelled on a fictitious cohort of 1000 women with the epidemiological and operating characteristics found in each country. The analysis also modelled the costs of doing single directed biopsy if a lesion had been visible during colposcopy and the cost of doing systematic 4-quadrant biopsy (as was done in the research). The cost per case detected was taken as the main indicator of cost-effectiveness. The base currency and year was US dollar in 2012 when the first round of screening was observed. For the HPV DNA test, it used the performance of Digene Hybrid Capture II (HC2), although the test costs were those observed for *careHPV* when it became available. The concordance of the two tests in our study population was verified to allow substitution of performance indicators.

The cost per case detected was least expensive using VIA/VILI in BF (\$205) and high grade cytology in SA (\$209). The incremental cost of using four-quadrant biopsy instead of directed biopsy as the confirmatory test was \$663 (with VIA/VILI in BF) and \$2333 (SA with low grade cytology) per additional case detected. While the range of costs per woman screened was less expensive in BF (US\$6-38) than SA (US\$34-111), the range of costs per case detected were more similar (US\$205-1284 vs. US\$209-2333 in SA), owing to higher CIN2+ prevalence and higher test sensitivity in SA. The costs per case detected were lower among women with CD4 \leq 200 (US\$86-538 in BF and US\$113-1256 in SA) as CIN2+ prevalence increased to 13.6% in BF and 41.7% in SA. *careHPV* was the most expensive screening visit (US\$20 in BF; US\$32 in SA). *careHPV* would only become cost-effective in BF if the test components were US\$4 or less and it was used as a triage strategy after VIA/VILI with directed biopsy. In SA, *careHPV* would be as cost-effective as HSIL cytology (with both tests followed by colposcopy-directed biopsy) if additional cost savings of US\$4 were found in other aspects of the visit and laboratory procedure and the *careHPV* test components were donated for free. These observations have to be put also in the context of the possibly increased operational feasibility of implementing *careHPV* in a given setting, allowing for increased coverage of screening, and consequently, increased returns as the tests are being rolled out.

C5. Accuracy of HPV DNA qualitative testing (Digene HC2 and *careHPV*) vs. genotyping to detect high-risk HPV genotypes and cervical lesions in HIV-positive African women

The HARP project did not get donated *careHPV* kits in time when it performed its enrolment round, but got those kits later on. Meanwhile, we had to use a 'similar' test in the form of the Digene Hybrid Capture II (HC2) test from which *careHPV* is derived. Consequently, the study provided the opportunity to assess the performance of each of these HPV DNA qualitative assays in the same women at two time points (enrolment and M16) against genotyping, cytological and histological endpoints. However, in order to interpret results over time, it was important to conduct a study looking at the head to head comparability of Digene HC2 and *careHPV* using paired samples obtained in a subgroup of women at month 12.

In a first study, we established the comparability of HC2 and *careHPV* for hrHPV DNA detection in cervical samples from 149 HIV-1-infected African women, the hrHPV DNA detection rate was 37.6% and 34.9% by *careHPV* and HC2, respectively. Agreement between the two tests was 94.6% (95% CI 89.7%-97.7%) with a Kappa value of 0.88 (95% CI, 0.81-0.96) indicating an excellent agreement. *careHPV* may be considered as suitable as HC2 for cervical cancer screening in African HIV-seropositive women (Ngou et al, J Clin Microbiol 2013).

In a second study we compared the performance of HC2 performed at enrolment with genotyping with INNO-LiPA to detect cervical lesions, and the agreement of the tests to detect hrHPV. The study found, not surprisingly, that INNO-LiPA presents a higher analytical sensitivity than HC2 but HC2 presents a higher specificity for detecting CIN2+ or CIN3+. The negative predictive values of the two tests are very similar. It was concluded that HC2 being more specific would be suitable for cervical screening (Ngou et al, JAIDS 2014). When looking at the performance of HC2 to detect all hrHPV genotype detected by genotyping, the detection rate appeared dependent of hrHPV genotype. For example, nearly 100% of HPV58 cases were detected by HC2, whereas this proportion dropped to 50% or less for HPV 51, HPV 52 or HPV 39 (Ngou et al, JAIDS 2014).

Similarly, in a direct comparison between INNO-LiPA and *careHPV* at Month 16, the study found that there was 'fair' agreement (kappa 0.25) between *careHPV* and INNO-LiPA, but agreement increasing to almost 'perfect' (kappa 0.87) in the group of women with high-grade cervical lesions. INNO-LiPA still presented a higher analytical sensitivity than *careHPV* but *careHPV* presented a higher specificity for the diagnosis of high-grade lesions. Both assays presented a high negative predictive values (>99%). Owing to its higher specificity and high NPV, *careHPV* may be considered suitable for cervical cancer screening in HIV-infected women in Africa. These results confirmed the previous findings with HC2 and the general good comparability of the two tests (Segondy et al, manuscript to be submitted). Importantly, these findings allowed the use of the results of the HPV DNA tests rather interchangeably.

C6. In conclusion

- 1) The risks for cervical cancer in women living with HIV are very high, although prevalence varies by country and by CD4 count. Being on ART alone does not reduce the risk of HR-HPV or CIN2+, but duration of ART, high CD4 and virological control can help decrease risk, highlighting the importance of good and sustained virological control and immune restoration provided by ART to control hrHPV natural history.
- 2) Over 80% of cervical lesions identified could be prevented with the next generation HPV vaccine which targets 7 of the main cancer causing HPV types.
- 3) Performance of screening tests: in South Africa, the current recommended screening tests (cytology) appear to perform reasonably well, while in Burkina Faso, the addition of HPV test would appear beneficial. Screening tests are most sensitive among women with CD4+ count below 200 cells/ μ L, and screening strategies may need to be further modified according to CD4+ count.
- 4) Choice of HPV DNA tests: compared with genotyping, both qualitative tests (Digene HC2 and *careHPV*) appear equivalently suitable because of their high specificity for specificity for detecting CIN2+ or CIN3+. The negative predictive values of the two tests are similar. *CareHPV* may have a better implementability and cost profile for low-resource countries, although our economic analysis suggests that *careHPV* should be offered at very low price (e.g. \$4) to be as cost-effective as the very cheap visual inspection with VIA/VILI promoted in Burkina Faso. *careHPV* as a triage test would be useful in allowing cost savings from fewer biopsies.

- 5) The most cost-effective cervical cancer screening strategy for women attending HIV clinics will vary by setting. Programs may want to consider targeting women with lower CD4 counts due to higher CIN-2+ prevalence. Depending on the setting, careHPV will not be a cost-effective option unless the price of test components are reduced or donated.

C7. Other lessons learned

The results of the two EPCs have underscored the importance of a rigorous review of cases by consensus panel – and shown that there was little chance of under diagnosing cases, hence minimising the possible misclassification bias when there was no indication for biopsy by protocol. Moreover, it has proven to be an important aspect of quality enhancement of the study as marked improvement in consistency of gradings between local pathologists and consensus teams.

D. POTENTIAL IMPACT, DISSEMINATION ACTIVITIES AND THE EXPLOITATION OF RESULTS

D1. Strategic impact

Cervical cancer, aetiologically linked for 99% to infection with oncogenic (high-risk) genital HPV contributes to substantial mortality worldwide. The cancer has particularly high incidence and mortality rates among African women, who do not have access to regular screening programme. Therefore, cervical cancer has an especially profound societal impact because it primarily affects women from their 30's to 50's, who are often raising or supporting families. Moreover, cervical cancer incidence is even greater among HIV-infected women. The impact due to cancer mortality has not been seen in the early stages of the AIDS epidemic in Africa (whilst cervical cancer has been recognised opportunistic cancer in the West). This is because of the tremendously high rates of HIV mortality in Africa in the absence of access to antiretroviral therapy. This is about to change possibly, thanks to the extension of ART programmes, affording longer survival to infected women, with ironically a greater likelihood to have longer persistence of hrHPV and the potential to develop neoplasia. High-risk HPV genotypes are associated with cervical neoplasia in >99% of cases and these genotypes can be detected with new rapid low-cost point-of care diagnostic assays, which raises the prospect to considerably enhance the coverage of screening and the impact of screening programmes.

The rapid extension of antiretroviral programmes across sub-Saharan Africa affords the opportunity to integrate a range of sexual and reproductive health (SRH) services and to assess their performance and impact on the morbidity, mortality and quality of life of HIV-infected patients. Conversely, the frequent and intensive follow-up of patients at HIV clinics provides an opportunity to study the effects of HIV-related factors and HAART on outcomes, such as cervical neoplasia, in these populations. Prevention of cervical cancer should rank high as a public health priority in sub-Saharan Africa. However, there are few functional screening programmes across the continent and in particular there are currently no definitive guidelines on how best to manage HIV-infected women in terms of screening strategies, interval and frequency of screening and management. The use of simplified HR-HPV DNA tests such as *careHPV*, which has never been evaluated in Africa, alone or combination with other tests in various triage strategies will improve the coverage of cervical cancer screening in these populations and will represent a cost-effective cervical cancer prevention interventions.

HARP has determined the incidence of CIN2+ in HIV infected women at all stages of their infection randomly recruited from HIV care centres, assessed a new diagnostic test (*careHPV*) and determined the HPV incidence, persistence and clearance. The combination of studies involved cohorts in South and West Africa. There are limited data on HIV and HPV from Africa and it is important to determine prevalence of HPV-types and predictors of cervical neoplasia in the context of HIV and ART in Africa. The new diagnostic test, if predictive may provide a tool to enhance detection and management of HIV-infected women in Africa at risk for cervical cancer. Overall, this study contributed important information on HPV in HIV for clinicians managing HIV infected women in care programmes.

In total, 1249 HIV positive women were recruited from HIV care centres in Burkina Faso and South Africa and were enrolled in a longitudinal cohort of 1107 women without CIN2. Women in the longitudinal study were followed for 16-months to determine incidence of CIN2+, and incidence, persistence and clearance of hrHPV infection. Modelling and economic analyses were performed to allow the development and validation of screening algorithms using locally-relevant epidemiological and economic data rarely available from Africa.

Our Consortium represented a strong collaborative inter-disciplinary team tackling a topic of compelling public health relevance in the African context of the 21st century. The issues

considered – HIV, ART, HPV-diagnostics and their predictive value – were pragmatic and yielded useful information for future regional efforts. The addition of a validated low cost rapid HPV detection kit (*careHPV*) could result in substantial improvements in cervical cancer prevention in resource poor settings, in particular for HIV positive women.

Innovation: The study has involved the use of some innovative assays (evaluation of *careHPV*) and has assessed HPV-HIV in cohorts from Africa, a region with limited data on HPV. The effect of HIV and ART on incidence, persistence, and clearance of HPV-type specific infection will be analysed and published in the post project period.

Investigators: The team had broad and complementary expertise with demonstrated proficiency in recruitment, enrolment, retention, and laboratory testing in addition to specific expertise in HPV molecular studies. The study involved extensive international collaboration – with cohorts at two African sites (University of Ouagadougou and WITS-WRHI), HPV genotyping at University of Montpellier 1, and study coordination and leadership from LSTHM. Our highly experienced research team has an already excellent record of collaboration.

The inclusion of West and South African cohorts allowed for broader regional impact.

D2. The use and dissemination of foreground

Apart from the activities jointly undertaken within the framework of the dissemination plan, the individual participants also have, through their networks and collaborations, ample opportunities for dissemination to all relevant stakeholders, specifically the scientific community, policy makers, the general public and industrial companies (e.g. Qiagen, GSK, Merck). The project has been invited to present its findings at an African regional meeting convened by Qiagen in Kenya in 2015.

The overall results of the project will be presented in a series of communication events targeting particular policy-making bodies at national level. In South Africa, the collaborative work continues through an MRC (UK) grant which investigates the feasibility of HPV vaccination among WLHIV and will use HARP findings to be presented to national policy makers. These stakeholders meetings will include members of the scientific community and organisation of WLHIV and other advocacy groups.

The consortium members participated in a variety of global networks in the area of HIV, HPV and Cervical Cancer as well as in the wide community of biomedical sciences and collaborate in large (inter)national research projects. This has provided excellent opportunities to disseminate the scientific output of HARP to the scientific community. Over 30 oral and poster presentations were made at international and national/regional conferences – and one of the African investigators won a prize at the ICASA/HIV conference in Cape Town.

D3. Management of intellectual property

An initial dissemination plan was developed by the management team in which the envisaged research results were described and regularly updated, together with the appropriate description of dissemination channels and target audiences. This Dissemination Plan and subsequent plans of analyses and publications plans were used as roadmap for exploitation and dissemination activities. A number of conferences were visited by more than one Consortium partner for maximum representation.

D4. Project website

The HARP project website consisted of two main areas, one aimed at the general public and the other for researchers (which includes Consortium staff and associated members). The open-access website, available in English and French, focused on:

- Partners in the Consortium, profiles of key scientists
- Project background, aims and objectives
- Project progress and results
- Project publications, conference presentations, seminar proceedings and slideshows
- Project annual/semi-annual Newsletter, Factsheets, Research Briefs and Policy Briefs
- Any training resources that would be useful beyond the project
- Links to the Partners websites

The website acknowledged the European Commission's FP7 support and displayed the EU flag and FP7 logo. There was a secure area for document sharing, an online forum for partner discussion, and Communities of Practice, which were reserved to share documents, CRFs, SOPs, tools and databases and papers.

E. HARP CONTACT DETAILS

For more information on HPV in Africa Research Partnership (HARP), please contact:

Frankie Liew, HARP Consortium Manager

London School of Hygiene & Tropical Medicine (LSHTM)

Faculty of Infectious and Tropical Diseases (ITD)

Department of Clinical Research (CRD)

Keppel Street, London, WC1E 7HT, UK

Tel: +44 20 7958 8235, Fax: +44 20 7436 5389

Email: frankie.liew@lshtm.ac.uk

Or, visit our website: www.harp-fp7.org