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▶ To cite this version:

Helen Kelly, Bernard Sawadogo, Admire Chikandiwa, Michel Segondy, Clare Gilham, et al.. Epidemiology of high-risk human papillomavirus and cervical lesions in African women living with HIV/AIDS. AIDS. Official journal of the international AIDS Society, 2017, 31 (2), pp.273 - 285. 10.1097/QAD.0000000000001301 . hal-01807971

HAL Id: hal-01807971

https://hal.science/hal-01807971v1

Submitted on 29 Oct 2020

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Epidemiology of High-risk Human Papillomavirus and Cervical Lesions in African women living with HIV/AIDS: Effect of Anti-Retroviral Therapy

Running title: HPV and CIN2+ in African women living with HIV-1

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Conflicts of Interest and Source of Funding:

The authors have no conflicts of interest to disclose.

Funding:

The research leading to these results has received funding from the European Commission (EC) 7th Framework Programme under grant agreement No. HEALTH-2010-F2-265396.

The *care*HPV and HC2 kits used in this project were obtained through the Qiagen Corporation donation program to the London School of Hygiene & Tropical Medicine.

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Abstract

Objective: To describe the effect of antiretroviral therapy (ART) and HIV-related factors on high-risk human papillomavirus (HR-HPV) and high-grade cervical intraepithelial neoplasia lesions (CIN2+) among women living with HIV/AIDS (WLHA) in sub-Saharan Africa**.**

Design: Prospective cohort of WLHA in Ouagadougou, Burkina Faso (BF) and Johannesburg, South Africa (SA). Recruitment was stratified by ART status.

Methods: At baseline and endline (median 16 months), cervical samples and biopsies were analyzed for HPV genotyping (InnoLiPA) and by histology. Logistic regression was used to estimate associations of ART and HIV-related factors with HR-HPV and CIN2+ outcomes, and all results presented are adjusted for baseline CD4+ count.

Results: Among 1238 enrolled WLHA (BF=615; SA=623), HR-HPV prevalence was 59.1% in BF and 79.1% in SA. CIN2+ prevalence was 5.8% in BF and 22.5% in SA. Compared to long-duration ART users (>2 years), HR-HPV prevalence was higher among short-duration ART users (≤2 years; aPR=1.24, 95%CI:1.04-1.47) in BF, and CIN2+ prevalence was higher among short-duration ART users (aOR=1.99, 95%CI:1.12-3.54) and ART-naïve participants (aOR=1.87, 95%CI:1.11-3.17) in SA. Among 963 (77.8%) women seen at endline, HR-HPV persistence was 41.1% in BF and 30.2% in SA; CIN2+ incidence over 16-months was 1.2% in BF and 5.8% in SA. HR-HPV persistence was associated with being ART-naïve in BF (aPR=1.89, 95%CI:1.26-2.83), and with short-duration ART use (aPR=1.78, 95%CI:1.11-2.86) and HIV-1 PVL ≥1000 copies/ml (aPR=2.87, 95%CI:1.63-5.05) in SA. CIN2+ incidence was reduced among women on ART in SA (aOR=0.39, 95%CI:0.15-1.01).

Conclusion: Prolonged and effective ART is important in controlling HR-HPV and the development of CIN2+.

Key words: HIV-1; human papillomavirus (HPV); cervical intraepithelial neoplasia (CIN); CD4, plasma viral load (PVL); antiretroviral therapy (ART); Africa

INTRODUCTION

Cervical cancer is the most common female cancer in low and middle-income countries [1], and one of the most common cancers in women living with HIV/AIDS (WLHA) [2]. Persistent infection with high-risk human papillomavirus (HR-HPV) genotypes is necessary for the development of squamous intraepithelial lesions (SIL) and cervical intraepithelial neoplasia (CIN) [3]. WLHA have higher prevalence of genital HR-HPV infection than the general population [4, 5], are more likely to be infected with multiple high risk types [6], have persistent infection [7] and have a higher risk of CIN progression [8].

The interactions of anti-retroviral therapy (ART) with HR-HPV and CIN are complex [9, 10]. ART increases potential exposure time to HR-HPV by decreasing mortality and increasing life-expectancy of WLHA, allowing for accumulation of cellular genetic changes that increase the likelihood of cervical disease [11, 12]. Improved survival among WLHA may thus lead to increased cervical cancer rates [9]. Conversely, by decreasing HIV plasma viral load (PVL), ART can restore mucosal immune competence to help clear HR-HPV and reduce the incidence of precursor lesions [13, 14]. Some studies show that "effective" ART (i.e. with high adherence, HIV viral suppression and immune reconstitution) over longer durations decreases HR-HPV prevalence [13, 15, 16], by decreasing incidence [17, 18] and promoting clearance [13, 17, 19]. ART has also been shown to reduce high-grade cytological squamous intraepithelial lesion incidence [20] and progression [21, 22] especially among adherent users [17] and those with sustained HIV viral suppression [23]. However, other studies have reported no such benefits of ART on HR-HPV [24, 25] or histological lesions [15, 26-30], with some reporting a significant increased risk of high-grade CIN (CIN2+) among ART users [31].

Few longitudinal studies have reported the effect of ART and other HIV-related factors on the combined natural history of HR-HPV infection and histological cervical lesions. An improved understanding of the effects of ART, virological control and immune recovery on the natural

history of HR-HPV infection and CIN progression would help tailor screening guidelines for high-risk populations.

We conducted a study of cervical cancer screening in a cohort of WLHA in Burkina Faso and South Africa (*HARP - HPV in Africa Research Partnership*). In this paper, we describe (i) the prevalence and persistence of HR-HPV infection; (ii) the prevalence and incidence of CIN2+; and (iii) the associations of these outcomes with ART and HIV-related factors (CD4+ count and HIV-1 PVL).

MATERIALS AND METHODS

Study population

Participants were recruited from the HIV outpatient clinic of the University Teaching Hospital of Ouagadougou, Burkina Faso (BF), and HIV treatment centres and surrounding communities in Johannesburg, South Africa (SA) from December 2011 to October 2012. Inclusion criteria were being HIV-1 seropositive, aged 25-50 years and resident in the city. Exclusion criteria were history of prior treatment for cervical cancer, previous hysterectomy, and being pregnant or less than 8 weeks postpartum. Enrolment was stratified in a 2:1 ratio of ART-users:naïve. At enrolment, eligibility for ART initiation in both countries followed the 2010 WHO guidelines with a CD4+ count threshold of 350 cells/mm^3 [32]. Written informed consent was obtained at the screening visit when eligibility for the study was assessed and at enrolment. Data on clinical, socio-demographic and behavioural characteristics were collected by interviewer-administered questionnaire. Participants were followed-up every 6 months for CD4+ counts up to month 18 (endline) when procedures similar to baseline were repeated.

Specimen collection

At enrolment, a venous blood sample was collected to confirm HIV-1 serostatus if needed, to perform HSV-2 and syphilis serologies and to obtain baseline HIV-1 RNA PVL and CD4+ counts. Urine

pregnancy testing was performed. Cervical samples were collected using a Digene cervical sampler (Qiagen, Courtaboeuf, France) for HPV-DNA testing and genotyping; a cytobrush for Papanicolaou smear cytology; and a swab from the ecto/endocervix to detect cervical sexually transmitted infections (STIs) by molecular methods. A vaginal smear was collected to diagnose bacterial vaginosis and *Candida albicans* by Gram stain. Participants were assessed clinically using visual inspection with acetic acid or Lugol's iodine (VIA/VILI). All participants were referred for colposcopy performed by trained colposcopists. Systematic 4-quadrant cervical biopsy, including directed biopsy of any suspicious lesions, was performed for participants who had abnormalities detected by cytology, VIA/VILI or colposcopy, or who were HR-HPV DNA positive (Digene HC-II). The same genital sampling and examination procedures were repeated at the endline visit at Month 18.

Laboratory testing

HIV-1 serostatus was diagnosed according to national guidelines [33, 34]. HSV-2 serology was performed using the Kalon® gG2 ELISA (Kalon Diagnostics, UK) and syphilis serology by a combination of a *Treponema pallidum* haemagglutination (TPHA) and rapid plasma reagin (RPR; BioMérieux, Lyon, France in BF; Immutrep carbon antigen RPR, Omega Diagnostics in SA). Plasma HIV-1 RNA was assessed using real-time PCR (Abbott RT HIV-1) in BF and COBAS Taqman (Roche Diagnostics) in SA, with a lower limit of detection of 40 copies/ml. Testing for CD4+ T-lymphocytes was performed using FACScount (Becton-Dickinson, NJ). Laboratories subscribed to international external quality assessment schemes; UK-NEQAS for CD4+ counts [35] and QCMD for HIV-1 PVL testing [36].

Neisseria gonorrhoeae, Chlamydia trachomatis, Mycoplasma genitalium and *Trichomonas vaginalis* were detected using nucleic acid amplification tests, the Sacace simplex assays (Sacace, Como, Italy) in BF and the APTIMA Combo (Gen-Probe, San Diego, CA) in SA. The Nugent's score [37] was

used for vaginal flora reading of Gram-stained vaginal smears, with diagnosis of bacterial vaginosis made for scores ≥7, and examined for the presence of *Candida spp*.

HR-HPV testing was performed at the University of Montpellier virology laboratory using the qualitative Digene HC-II (Qiagen, Gaithersburg, MD) and genotyping with the INNO-LiPA HPV genotyping Extra® assay (Innogenetics, Courtaboeuf, France)[38, 39]. HR-HPV types were defined using the current International Agency for Research on Cancer (IARC) classification [40]: 'carcinogenic to humans' (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59) and 'probable carcinogenic' (HPV68).

Cervical biopsies were processed at the local pathology laboratories in Ouagaoudou and Johannesburg and read using the 3-tier CIN classification system [41]. Histology was classified as 'negative' (≤CIN1) or 'positive' (CIN2+) based on the highest reading across all findings from the 4-quadrant biopsies and endocervical curettage if collected. All histological slides from women with a local diagnosis of CIN2+ and approximately 10% of slides from women with ≤CIN1 histological findings were reviewed by the HARP Endpoint Committee of five pathologists, for consensus classification.

Statistical analysis

HR-HPV type-specific persistence was defined as being positive for the same type at baseline and endline by genotyping. Type-specific clearance was defined as being positive for a specific HR type at baseline and negative for the same type at endline, while complete clearance was defined as being positive for at least one HR type at baseline and negative for all HR types at endline. As HR-HPV prevalence was common, associations with exposure variables were estimated with prevalence ratios (PRs) obtained from logistic regression using marginal standardization to estimate PRs, and the delta method to estimate 95% confidence intervals (CI) [42]. Associations between HR-HPV persistence and exposure variables were estimated with generalised estimating

equation to account for multiple HR-HPV infection and multiple infection states (persistence and clearance) [43]. For associations with CIN2+ prevalence and incidence over 16 months, logistic regression was used to estimate odds ratios (ORs) and 95%CI.

Multivariable analyses were adjusted for site and socio-demographic and behavioural factors which were independently associated in univariate analyses ($p<0.10$) with HR-HPV or CIN2+ for each country (Model 1). To explore associations of HR-HPV and CIN2+ outcomes with HIV-related factors, pre-specified analyses included stratification by site, ART use and duration (≤ or > 2 years), HIV-1 viral suppression (< or ≥1000 copies/ml) and CD4+ counts. Stable high CD4+ count was defined as having CD4+ counts >500 cells/mm^3 at baseline, month 12 and endline visits. A second logistic regression model (Model 2) incorporated baseline CD4+ count to Model 1 to explore associations with ART. Data were analysed using Stata version 14 (Stata Statistical Software, College Station. TX: Stata Corporation).

Ethical approval was granted by the Ministry of Health in Burkina Faso (no. 2012-12-089), the Witwatersrand University in South Africa (no. 110707), and the London School of Hygiene and Tropical Medicine (no. 7400).

RESULTS

Study population

Of 1473 women screened, 1238 were enrolled (BF:615; SA:623; **Figure 1**). The median age of participants was 36 (interquartile range [IQR], 31-41) years in BF and 34 (IQR, 30-40) years in SA (**Table 1**). Participants in BF had lower levels of education and were less likely to be employed than those in SA. Classical risk factors for HR-HPV and CIN, including smoking, hormonal contraception use and higher number of sexual partners, were more prevalent in SA than BF, as were all STIs, except *Candida* infection. About half (49.6%) of SA participants had ever had a Pap smear, and a

fifth (20.8%) of BF participants had ever had a VIA/VILI examination, the primary cervical cancer screening modality in each country, respectively.

At enrolment, 422 (68.6%) participants were on ART in BF and 406 (65.2%) in SA, reflecting the 2:1 stratification ratio. There were 126 women in BF and 22 in SA who initiated ART in the month prior to enrolment. The median duration on ART was 17 (IQR, 0-63) months in BF and 28 (IQR, 10-50) months in SA. The median CD4+ count among ART-naive and ART users was 417 (IQR, 315-606) cells/mm^3 and 446 (IQR, 309-600) cells/mm^3 respectively, in BF and 448 (IQR, 353-614) cells/mm^3 and 420 (IQR, 279-567) cells/mm^3 in SA. HIV-1 RNA was undetectable ($\leq$40 copies/ml) in 69.9% and 33.7% of ART users in BF and SA, respectively, while HIV-1 RNA suppression (<1000 copies/ml) was 79.9% and 80.3% among ART users in BF and SA, respectively. Overall, 32 participants (BF:24; SA:8; 2.6%) denied being on ART at enrolment despite undetectable HIV-1 PVL. Of these, 23 (72%) had CD4+ count >500 cells/mm^3. Given the uncertainty of their status, these women were excluded from HIV-related factors analyses.

Of the 1077 women without CIN2+ at baseline, 963 (89.4%) were seen at endline visit (median follow-up 16 months, IQR, 15.6-16.8). Fifty-three women (10.4%) in BF and 25 (5.5%) in SA initiated ART during follow-up (**Table 2**). The median CD4+ count changes among ART users at baseline, ART initiators and those who remained ART-naive were +105, +123 and +65 cells/mm^3 per year respectively in BF, and +5, +83 and -53 cells/mm^3 per year respectively in SA. Genotyping data at both baseline and endline was available for 922 (95.7%) women (BF: 476; SA: 446) and histology results were available for 809 (84.0%) women (BF: 430; SA: 379) **(Figure 1).**

Prevalence and risk factors for HR-HPV at baseline

Of the 1238 participants enrolled, 1215 (98.1%) had valid HPV genotyping results (BF:96.6%; SA:99.7%) (**Figure 1**). HR-HPV prevalence was lower in BF than SA (BF:59.1% vs. SA:79.1%; p<0.001)

(**Table 1**). Overall, 1128 (91.1%) participants (BF: 90.1%; SA: 92.1%) had valid histology results (**Figure 1**). CIN2+ prevalence was 5.8% (32/554) in BF and 22.5% (129/574) in SA (p<0.001).

HR-HPV prevalence was higher among those with low CD4+ count in both countries (**Table 3**) and this association was strongest among ART users (CD4+ count <200 vs. >500 cells/mm^3, adjusted Prevalence Ratio [aPR]=1.30, 95%CI: 1.13-1.49, adjusted for site).

Compared to long-duration ART users (>2 years), HR-HPV prevalence was higher among those on short-duration ART in both countries (≤2 years), however when adjusted for CD4+ count, this association was observed in BF only (65.1% vs. 52.1% for ≤2 years compared to >2 years; aPR=1.24, 95%CI: 1.04-1.47, **Table 3**). There was weak evidence of higher HR-HPV prevalence among ART-naïve compared to long-term ART users in both countries (**Table 3**).

Association of HR-HPV persistence with ART and HIV-related factors

Among 610 women without CIN2+ but HR-HPV positive at baseline, the total number of baseline infections was 1028 (BF: 416; SA: 612; **Table 2**). Persistent infection of an HR-HPV type at endline was slightly higher in BF (BF: 41.1% vs. SA: 30.2%; p<0.001, **Table 2**).

HR-HPV persistence was associated with low baseline CD4+ count in BF only and this association was strongest among ART users (CD4+ count <200 vs. >500 cells/mm^3, aOR=1.85, 95%CI: 1.15-2.96, Model 1, **Table 4**). HR-HPV persistence was higher among ART-naive compared to long-duration ART users in both sites (Model 1, **Table 4**). However, when adjusted for baseline CD4+ count (Model 2, **Table 4**), the association persisted in BF only (58.6% vs. 37.7%; aOR=1.89, 95%CI: 1.26-2.83). In SA, HR-HPV persistence was higher among short-duration compared to long-duration ART users even after adjustment (aOR=1.78, 95%CI: 1.11-2.86; Model 2, **Table 4**).

Among ART users in SA, HR-HPV persistence was associated with lack of HIV-1 viral suppression at baseline (49.3% vs. 24.8% for women with PVL ≥1000 copies/mL vs. <1000 copies/ml; aOR=2.87, 95%CI: 1.63-5.05).

Among participants who remained ART-naive throughout the follow-up period, women with unstable CD4+ count or stable low CD4+ count (≤500 cells/mm^3) had increased likelihood of persistence compared to those with stable high CD4+ count (>500 cells/mm^3; both sites combined: 40.9% vs. 25.8%) but the association was not statistically significant after adjustment (aOR=1.83, 95%CI: 0.74-4.52, adjusted for site).

Association of CIN2+ prevalence and incidence with ART and HIV-related factors

CIN2+ prevalence was higher among participants with low baseline CD4+ count in both countries (**Table 3;** combined effect: CD4+ count <200 vs. >500 cells/mm^3, aOR=3.45, 95%CI: 1.89-6.28, adjusted for site; data not shown) and this association was strongest among ART users (both countries combined: aOR=4.29, 95%CI: 2.16-8.50). Among ART-naive, CD4+ count below the threshold for ART initiation according to the 2010 WHO guidelines was associated with higher risk of CIN2+ in SA only (≤350 vs. >350 cells/mm^3 38.0% vs. 20.4%; aOR=2.49, 95%CI: 1.12-5.53; data not shown).

CIN2+ prevalence was higher among participants on short-duration ART (≤2 years) and among ART-naïve compared to long-duration ART users in SA and these associations persisted after adjustment for baseline CD4+ count (ART≤2 years vs. >2 years: aOR=1.99, 95%CI: 1.12-3.54; ART-naïve vs. ART >2 years: aOR=1.87, 95%CI: 1.11-3.17, **Table 3**).

The incidence of CIN2+ over 16 months was higher in SA (BF: 1.2% [5/430] vs.SA: 5.8% [22/379]; p<0.001; **Table 2**). There was weak evidence that CIN2+ incidence was lower among consistent ART users (i.e. on ART at both baseline and endline visit) compared to those who remained ART-naive in SA (4.4% vs 9.9%; aOR=0.39, 95%CI: 0.15-1.01, adjusted for number of lifetime sex partners and

baseline CD4+ count), but no association was observed in BF due to the small number of incident cases.

Association of CIN2+ with HR-HPV

Among 1119 women with genotyping and histology data at enrolment, prevalence of CIN2+ was significantly higher among those HR-HPV positive compared to HR-HPV negative (BF: 9.8% vs. 0.0%; SA: 25.7% vs. 10.2%; aOR=5.12, 95%CI:2.66-9.89, adjusted for site, CD4+ and ART). Among 780 women with genotyping and histology at baseline and endline, CIN2+ incidence over 16 months was higher among those with HR-HPV persistence compared to those who had type-specific clearance or who were HR-HPV negative at baseline (BF: 3.5% vs. 0.9%; SA: 13.4% vs. 2.6%; aOR=5.60, 95%CI:1.97-15.94; adjusted for number of lifetime sex partners, baseline CD4+ count and ART).

DISCUSSION

This large prospective study found high prevalence and persistence of HR-HPV among women living with HIV-1 in Burkina Faso and South Africa, and HR-HPV persistence was associated with incidence of CIN2+ over 16 months. Strikingly, CIN2+ prevalence and incidence were higher in South Africa despite balanced distribution of ART use, similar median duration on ART and median CD4+ counts at study enrolment in both countries, and similar HR-HPV persistence rates over 16 months.

We found that low baseline CD4+ count was associated with a higher prevalence of HR-HPV and CIN2+ in both countries, and with HR-HPV persistence in BF, similar to other studies that have shown CD4+ count to be one of the strongest predictors of HR-HPV infection [44] and cervical lesion development [45]. We also found that prolonged duration of ART was associated with lower CIN2+ prevalence and HR-HPV persistence, similar to others [13, 15, 46], and this association was independent of baseline CD4+ count. Although HR-HPV persistence was similar in both countries,

cervical lesion progression was higher in South Africa and this may have been influenced by the role of HIV-related and other cofactors, which differed between the two countries.

In Burkina Faso, prolonged and short-duration ART users had a similar risk of HR-HPV persistence when CD4+ counts were >500 cells/mm^3. However the risk was higher among short-duration compared to long-duration ART users when CD4+ count was low (<200 cells/mm^3). This suggests that once the recent ART initiators begin to recover CD4+ T-lymphocytes, they can control HR-HPV persistence, leading to the lower prevalence of CIN2+.

By contrast, in South Africa, short-duration ART users had higher persistence of HR-HPV and CIN2+ prevalence, irrespective of baseline CD4+ count. This may be a consequence of several factors. Firstly, ART users in South Africa were not as well HIV-controlled as their counterparts in Burkina Faso. Effective ART use, as measured by HIV-1 RNA suppression (PVL <1000 copies/ml), was associated with a decrease in HR-HPV persistence over 16 months in South Africa, independent of baseline CD4+ count. Others have shown that HR-HPV persistence was increased 2-3 fold among women (6% ART users) with detectable genital tract HIV RNA levels, after adjusting for CD4+ count but not when adjusted for plasma HIV [47], thereby suggesting a possible direct role of HIV on HR-HPV through both local and systemic mechanisms. The greater proportion of ART users in South Africa with detectable HIV PVL (65% in South Africa vs. 23% in Burkina Faso) may be a consequence of their poor self-reported adherence, which was observed among both short and long-duration ART users. Women with suboptimal adherence may have developed, or initially acquired, some antiretroviral-resistant HIV strain, although we cannot verify this in the absence of HIV genotyping. Secondly, ART use in the short-term may be ineffective in clearing HR-HPV if already well established. Others have shown that ART users are at a higher risk of cervical disease if they have initiated ART at a lower nadir CD4+ count [27, 48, 49]. In such cases, the CD4+ T-lymphocyte reconstitution accompanying ART may be partial or functionally impaired and the beneficial effects of ART may only become apparent after long treatment periods [12]. It is possible in our study that immune reconstitution achieved through recent ART initiation at the previous WHO cut-off of 350

cells/mm^3 may have been insufficient to prevent HR-HPV persistence and/or CIN2+ development, in particular when coupled with detectable HIV, lower ART adherence and lower CD4+ T-lymphocyte recovery over time, as was the case among women in South Africa. Early ART initiation, coupled with rapid virological control, is likely to rapidly improve and maintain CD4+ count at a higher level [50], leading to possibly more complete and sustained immune reconstitution, thereby reducing the risk of persistent HR-HPV and cervical lesion development. Finally, the higher CIN2+ prevalence and incidence in South Africa may additionally be explained by other cofactors for such as greater frequency of contraceptive use and smoking and higher prevalence of mucosal STIs [51-53]. The presence of STIs can trigger genital HIV replication, a cascade of mucosal immunological synergies and vaginal biome changes [54, 55], which may interact with HR-HPV [56]. Addressing such cofactors should also be a priority of cervical cancer prevention programmes.

Importantly, this study has found that ART use was associated with a reduction in incident CIN2+ over 16 months in South Africa. Furthermore, by endline, ART duration had increased to a median 44 months which may have played a role in averting CIN development.

ART-naïve women in South Africa had similar HR-HPV persistence and CIN2+ prevalence as prolonged ART users at high CD4+ (>500 cells/mm^3), but both outcomes worsened among the ART-naïve as CD4+ count decreased. This finding highlights the role of early ART initiation to favorably influence the natural history of HR-HPV and CIN.

This study was constrained by the absence of consistent data on nadir CD4+ count, absence of a HIV-1 PVL measure at the endline visit, and the limited number of intermediate visits and overall follow-up duration. Despite these limitations, this study had several strengths, including its longitudinal design, the availability of a rigorously validated histological endpoint for the majority of women thereby minimizing disease ascertainment bias; and the availability of genotyping data at both time points. Moreover, the HARP study was undertaken in two countries with different HIV epidemics, burdens of HPV infection and cervical cancer, and approaches to screening for

cervical cancer. This allows the findings to be extended to a range of countries and settings in the region.

In conclusion, this study confirms that women living with HIV-1 in sub-Saharan Africa have extraordinarily high rates of HR-HPV infection and CIN2+. Effective ART use over prolonged duration is essential in reducing HR-HPV persistence and CIN2+ incidence. Early ART initiation is likely to further reduce the risk of HR-HPV infection and incident cervical lesions. These data underscore the importance of cervical cancer screening and access to treatment in these highly exposed and vulnerable populations, and the need for close monitoring of both HIV-related and HPV/CIN parameters before or during ART treatment as part of a comprehensive cervical cancer prevention programme.

ACKNOWLEDGEMENTS

Contributing members of the HARP study group included: A. Chikandiwa, E. Cutler, S. Delany-Moretlwe, D. A. Lewis, M.P. Magooa, V. Maseko, P. Michelow, B. Muzah, T. Omar, A. Puren (Johannesburg, South Africa); F. Djigma, J. Drabo, O. Goumbri-Lompo, N. Meda, B. Sawadogo, J. Simporé, A. Yonli, S Zan (Ouagadougou, Burkina Faso); V. Costes, M.N. Didelot, S. Doutre, N. Leventoux, N. Nagot, J. Ngou, M. Segondy (Montpellier, France); and A. Devine, C. Gilham, L. Gibson, H. Kelly, R. Legood, P. Mayaud, H.A. Weiss (London, UK).

The HARP Study Group also wishes to thank its International Scientific Advisory Group (ISAG) constituting of Prof. C. Lacey (Chair, University of York, UK), Prof. Y. Qiao (Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China), Prof. M. Chirenje (University of Harare, Zimbabwe) and Prof. S. de Sanjosé (Institut Catala d'Oncologia, Barcelona, Spain); and the members of the HARP Endpoint Committee (EPC) including T. Omar (Johannesburg, South Africa), O. Goumbri-Lompo (Ouagadougou, Burkina Faso), S. Doutre, N. Leventoux, V. Costes (Montpellier, France) and O. Claveros (Institut Catala d'Oncologia, Barcelona, Spain).

The research leading to these results has received funding from the European Commission (EC) 7th Framework Programme under grant agreement No. HEALTH-2010-F2-265396.

The research findings were presented at the 30th International Papillomavirus Conference 17-21 September 2015, abstract number HPV15-0792; and the 8th International Francophone Conference VIH/Hépatites AFRAVIH 2016 20-23 April 2016, abstract number S11.O1

AUTHOR CONTRIBUTIONS

Conceived and designed the study: PM, SD, NM, HW, MS, NN; Coordinated the study: HK, BS, AC, NM, SD, PM; Participant recruitment and management: BS, AC, NM, SD; Performed the lab testing: JN, OL, TO, MND; Analysed the data: HK, HW, CG; Wrote the first draft of the manuscript: HK, HW, PM; Contributed to the writing of the manuscript: HK, HW, PM, MS, NN, SD; Criteria for authorship read and met: HK, BS, AC, MS, JN, OL, TO, CG, MND, NN, NM, SD, HW, PM; Agree with manuscript results and conclusions: all.

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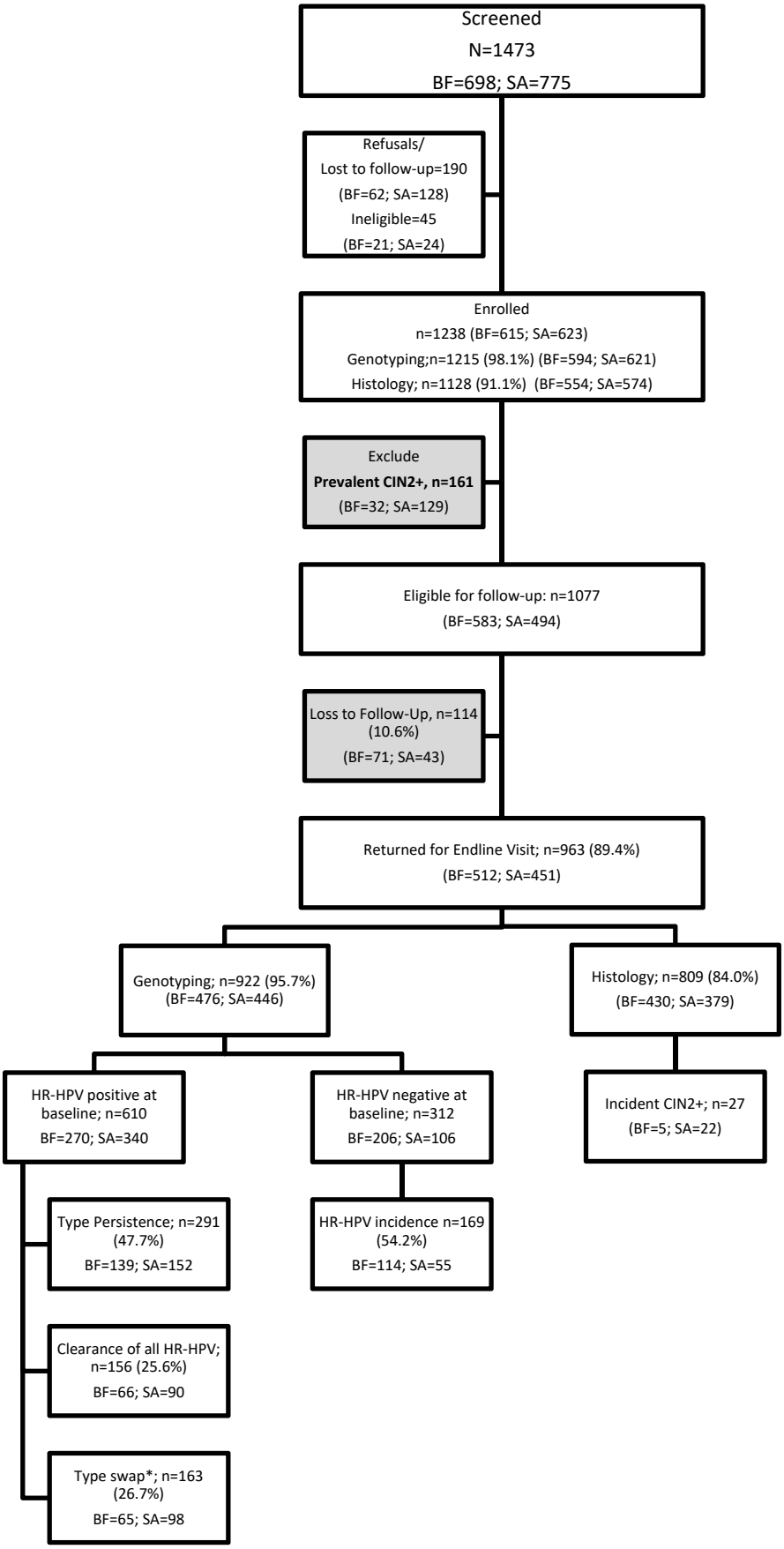
Figure 1 Study flowchart



*Type swap is defined as clearance of one genotype and acquisition of a different genotype

Table 1: Study population characteristics at baseline visit

	Burkina Faso N=615		South Africa N=623		p-value
	n or median	(%) or [IQR]	n or median	(%) or [IQR]	
Sociodemographic					
Age-years	36	(31, 41)	34	(30, 40)	<0.001
Education					<0.001
No schooling	268	(43.6)	7	(1.1)	
Primary/Incomplete secondary	324	(52.7)	349	(56.0)	
Completed secondary	15	(2.4)	249	(40.0)	
Graduate/postgraduate	7	(1.1)	18	(2.9)	
Not known	1	(0.2)	0	(0.0)	
Currently employed					<0.001
No	538	(87.5)	281	(45.1)	
Yes	77	(12.5)	342	(54.9)	
Marital status					<0.001
Never married	74	(12.0)	318	(51.0)	
Divorced/separated	95	(15.4)	23	(3.7)	
Widowed	143	(23.3)	18	(2.9)	
Married/cohabiting	302	(49.1)	264	(42.4)	
Not known	1	(0.2)	0	(0.0)	
Ever Smoke					<0.001
Never	610	(99.2)	545	(87.5)	
Ever	5	(0.8)	78	(12.5)	
Alcohol use					0.12
Never	409	(66.5)	432	(69.3)	
Sometimes but <Monthly	141	(22.9)	146	(23.4)	
At least monthly	65	(10.6)	45	(7.2)	
Age at first pregnancy-years	20	(18, 22)	20	(18, 22)	0.12
Number of pregnancies	3	(2,5)	2	(2,3)	<0.001
Number of live births	2	(1,4)	2	(1,3)	<0.001
Ever used Hormonal contraception					<0.001
No	105	(17.1)	23	(3.7)	
Yes	313	(50.9)	535	(85.9)	
Not known	197	(32.0)	65	(10.4)	
Injectable contraception					<0.001
No	487	(79.2)	173	(27.8)	
Past or current	123	(20.0)	450	(72.2)	
Not known	5	(0.8)	0	(0.0)	
Oral contraception					0.23
No	446	(72.5)	428	(68.7)	
Past or current	165	(26.8)	195	(31.3)	
Not known	4	(0.7)	0	(0.0)	
Condom use					<0.001
Never	62	(10.1)	53	(8.5)	
Ever	448	(72.9)	547	(87.8)	
Not known	105	(17.1)	23	(3.7)	
Sexual behaviour					
Age at first sex-years	18	(17, 19)	18	(16, 19)	0.01
Lifetime sex partners					<0.001
1	143	(23.3)	17	(2.7)	
2-4	406	(66.0)	284	(45.6)	
5+	66	(10.7)	228	(36.6)	
Not known	0	(0.0)	94	(15.1)	
Number of partners in last 3 months					<0.001
0	224	(36.4)	111	(17.8)	
1	374	(60.8)	475	(76.2)	
≥2	17	(2.8)	35	(5.6)	
Not known	0	(0.0)	2	(0.3)	
Ever cleanse vagina					<0.001
No	3	(0.5)	353	(56.7)	
Yes	242	(39.4)	253	(40.6)	
Sometimes	370	(60.2)	17	(2.7)	
Cervical cancer screening					
Ever had Pap smear					<0.001
No	541	(88.0)	313	(50.2)	
Yes	72	(11.7)	309	(49.6)	
Not known	2	(0.3)	1	(0.2)	

	Burkina Faso N=615		South Africa N=623		p-value
	n or median	(%) or [IQR]	n or median	(%) or [IQR]	
Ever had visual inspection (VIA/VILI)					<0.001
No	487	(79.2)	588	(94.4)	
Yes	128	(20.8)	16	(2.6)	
Don't know	0	(0.0)	19	(3.1)	
HIV related factors					
Median duration since HIV diagnosis (years)	5	(2,8)	4	(2,7)	0.03
ART status at enrolment*					0.01
ART >2 years	196	(31.9)	227	(36.4)	
ART ≤2 years	226	(36.8)	179	(28.7)	
ART-naïve	193	(31.4)	217	(34.8)	
Median duration on ART (months)	16.6	(0.0, 63.4)	28.1	(10.3.49.9)	0.002
Self-reported ART adherence (among ART users)					<0.001
>90%	0	(0.0)	0	(0.0)	
60-90%	387	(91.7)	339	(83.5)	
<60%	10	(2.4)	63	(15.5)	
Not known	25	(5.9)	4	(1.0)	
HIV-1 PVL suppression (<1000 copies/ml) among ART users					<0.001
No	56	(13.3)	76	(18.7)	
Yes	337	(79.9)	326	(80.3)	
Failed result	29	(6.9)	4	(1.0)	
HIV-1 PVL undetectable (≤40 copies/ml) among ART users					<0.001
No	98	(23.2)	265	(65.3)	
Yes	295	(69.9)	137	(33.7)	
Failed result	29	(6.9)	4	(1.0)	
HIV-1 PVL among ART-naïve, copies/ml	48,800	(10870, 206557)	19,300	(4680, 55400)	<0.001
Baseline CD4 count among ART users, cells/mm^3					0.18
>500	170	(40.3)	139	(34.2)	
351-500	121	(28.7)	114	(28.1)	
200-350	82	(19.4)	102	(25.1)	
<200	48	(11.4)	51	(12.6)	
Missing	1	(0.2)	0	(0.0)	
Baseline CD4 count among ART-naïve, cells/mm^3					0.01
>500	74	(38.3)	92	(42.4)	
351-500	51	(26.4)	72	(33.2)	
200-350	49	(25.4)	47	(21.7)	
<200	19	(9.8)	6	(2.8)	
Clinical signs and symptoms					
Cervical ectopy					<0.001
Normal	419	(68.1)	597	(95.8)	
<20% cervical surface	114	(18.5)	19	(3.1)	
≥20% cervical surface	79	(12.9)	7	(1.1)	
Not known	3	(0.5)	0	(0.0)	
Cervicitis					<0.001
No	409	(66.5)	508	(81.5)	
Yes	200	(32.5)	112	(18.0)	
Not known	6	(1.0)	3	(0.5)	
Anogenital warts					0.19
No	566	(92.3)	587	(94.2)	
Yes	47	(7.7)	36	(5.8)	
Laboratory STI					
Neisseria gonorrhoeae	4	(0.7)	14	(2.3)	0.02
Chlamydia trachomatis	13	(2.1)	31	(5.0)	0.01
Trichomonas vaginalis	-	-	101	(16.2)	
Mycoplasma genitalium	4	(0.7)	46	(7.4)	<0.001
Bacterial vaginosis	205	(34.6)	254	(41.6)	0.01
Candida albicans	87	(14.7)	52	(8.4)	<0.001
HSV-2 serology	459	(74.9)	590	(95.2)	<0.001
Active syphilis serology	1	(0.2)	7	(1.1)	0.02
HR-HPV					
HR-HPV positive	351	(59.1)	491	(79.1)	<0.001
CIN status					
Normal	373	(67.3)	261	(45.5)	<0.001
CIN1	149	(26.9)	184	(32.1)	
CIN2	19	(3.4)	76	(13.2)	
CIN3+	13	(2.4)	53	(9.2)	

*The study was designed to include two-thirds of participants on ART in each site

Table 2: Study population characteristics at endline visit

	Burkina Faso N=512		South Africa N=451		p-value
	n or median	**(%) or [IQR]**	**n or median**	**(%) or [IQR]**	
Duration of follow-up (FU)	16.4	[16.1-17.0]	15.9	[14.4-16.8]	
ART status at FU					0.002
ART users before enrolment	350	(68.4)	296	(65.6)	
ART initiators during FU	53	(10.4)	25	(5.5)	
ART naive at FU	109	(21.3)	130	(28.8)	
Median CD4+ count (cells/mm³) at M16					
ART users before enrolment	614	[434-819]	439	[322-604]	<0.001
ART initiators during FU	461	[312-613]	442	[366-601]	0.92
ART naive at FU	582	[439-868]	437	[346-543]	<0.001
Median CD4+ count (cells/mm³) change per year					
ART users before enrolment	105	(18, 207)	5	(-56, 88)	<0.001
ART initiators during FU	123	(35, 258)	83	(-50, 211)	0.17
ART naive at FU	65	(-24, 185)	-53	(-117, 21)	<0.001
Patients with stable high CD4+ count (>500 cells/mm³)					
ART users before enrolment	129	(36.9)	62	(21.0)	<0.001
ART initiators during FU	3	(5.7)	1	(4.0)	0.76
ART naive at FU	47	(43.1)	27	(20.8)	<0.001
HR-HPV status (number of women)	**N**	**n (%)**	**N**	**n (%)**	
HR-HPV persistence	270	139 (51.5)	340	152 (44.7)	0.10
HR-HPV complete clearance	270	66 (24.4)	340	90 (26.5)	0.57
HR-HPV clearance of any type	270	180 (66.7)	340	268 (78.8)	0.001
HR-HPV incidence of any type	476	228 (47.9)	446	220 (49.3)	0.67
HR-HPV incidence among HR-HPV negative at baseline	206	114 (55.3)	106	55 (51.9)	0.56
HR-HPV status (number of infections)	**N**	**n (%)**	**N**	**n (%)**	
HR-HPV persistence	416	171 (41.1)	612	185 (30.2)	<0.001
HR-HPV clearance	416	245 (58.9)	612	427 (69.8)	<0.001
HR-HPV clearance, in absence of persistence	416	189 (45.4)	612	295 (48.2)	
HR-HPV incidence		350		328	
CIN2+ Incidence	430	5 (1.2)	379	22 (5.8)	<0.001

Table 3. Effect of HIV related factors on HR-HPV and CIN2+ prevalence

	HR-HPV Prevalence								CIN2+ Prevalence							
	Burkina Faso N=570				South Africa N=613				Burkina Faso N=530				South Africa N=566			
	N	n (%)	Model 1[1] aPR (95% CI)	Model 2[2] aPR (95% CI)	N	n (%)	Model 1[1] aPR (95% CI)	Model 2[2] aPR (95% CI)	N	n (%)	Model 1[3] aPR (95% CI)	Model 2[4] aPR (95% CI)	N	n (%)	Model 1[3] aPR (95% CI)	Model 2[4] aPR (95% CI)
Baseline CD4+ count (cells/mm3)[§]																
<200	**66**	50 (75.8)	**1.43 (1.18-1.72)**	-	57	50 (87.7)	**1.15 (1.01-1.30)**	-	**57**	8 (14.0)	**2.99 (1.05-8.58)**	-	**50**	21 (42.0)	**3.46 (1.70-7.04)**	-
200-350	**125**	76 (60.8)	1.09 (0.90-1.33)	-	148	120 (81.1)	1.06 (0.96-1.19)	-	**116**	5 (4.3)	0.72 (0.23-2.21)	-	**138**	38 (27.5)	1.70 (0.98-2.93)	-
351-500	**161**	92 (57.1)	1.04 (0.87-1.26)	-	183	141 (77.1)	1.03 (0.92-1.14)	-	**151**	6 (4.0)	0.69 (0.24-2.01)	-	**174**	30 (17.2)	0.95 (0.55-1.63)	-
>500	**217**	119 (54.8)	1	-	225	172 (76.4)	1	-	**205**	13 (6.3)	1	-	**204**	39 (19.1)	1	-
ART status at baseline																
ART >2 years	**194**	101 (52.1)	1	**1**	**225**	163 (72.4)	1		**182**	10 (5.5)	1	**1**	**207**	31 (15.0)	1	1
ART ≤2 years	**218**	142 (65.1)	**1.29 (1.09-1.53)**	**1.24 (1.04-1.47)**	**179**	147 (82.1)	**1.12 (1.01-1.24)**	1.09 (0.98-1.22)	**206**	16 (7.8)	1.44 (0.59-3.54)	1.22 (0.48-3.08)	**161**	47 (29.2)	**2.56 (1.50-4.39)**	**1.99 (1.12-3.54)**
ART-naive	**158**	95 (60.1)	1.17 (0.96-1.43)	1.13 (0.92-1.38)	209	173 (82.8)	1.11 (1.00-1.23)	1.10 (1.00-1.22)	**142**	6 (4.2)	1.33 (0.42-4.25)	1.20 (0.37-3.94)	**198**	50 (25.3)	**1.86 (1.11-3.12)**	**1.87 (1.11-3.17)**
Among ART users:																
HIV-1 viral suppression[†]																
<1000 copies/ml	**328**	196 (59.8)	1	1	**324**	246 (75.9)	1	1	**309**	22 (7.1)	1	1	**294**	62 (21.1)	1	1
≥1000 copies/ml	**55**	32 (58.2)	0.98 (0.77-1.25)	0.81 (0.59-1.12)	**76**	62 (81.6)	1.01 (0.88-1.17)	0.99 (0.85-1.15)	**52**	4 (7.7)	1.45 (0.43-4.89)	0.55 (0.12-2.45)	**71**	15 (21.1)	1.08 (0.56-2.09)	0.85 (0.43-1.71)
ART adherence[‡]																
Moderate adherence (60-90%)	**378**	223 (59.0)	1	1	**337**	253 (75.1)	1	1	**358**	26 (7.3)	1	1	**311**	64 (20.6)	1	1
Low Adherence (<60%)	**10**	7 (70.0)	1.12 (0.70-1.79)	1.06 (0.62-1.79)	**63**	54 (85.7)	1.11 (0.98-1.27)	1.10 (0.96-1.26)	**7**	0 (0.0)	-	-	**53**	13 (24.5)	1.36 (0.67-2.76)	1.29 (0.62-2.69)
Baseline CD4+ count (cells/mm³)[§]																
<200	**47**	36 (76.6)	**1.48 (1.19-1.84)**	-	**51**	45 (88.2)	**1.18 (1.01-1.37)**		**42**	7 (16.7)	**4.34 (1.25-15.10)**		**45**	19 (42.2)	**4.30 (1.89-9.76)**	
200-350	**80**	50 (62.5)	1.15 (0.92-1.45)	-	**102**	83 (81.4)	1.10 (0.95-1.26)		**76**	4 (5.3)	1.10 (0.29-4.13)		**92**	20 (21.7)	1.27 (0.62-2.61)	
351-500	**119**	68 (57.1)	1.05 (0.84-1.30)	-	**113**	81 (71.7)	0.99 (0.86-1.15)		**113**	6 (5.3)	1.03 (0.31-3.39)		**107**	16 (15.0)	0.84 (0.41-1.72)	
>500	**165**	88 (58.3)	1	-	**138**	101 (73.2)	1		**156**	9 (5.8)	1		**124**	23 (18.6)	1	
Among ART-naïve:																
Baseline CD4+ count (cells/mm³)																
<200	**19**	14 (73.7)	1.20 (0.81-1.78)		**6**	5 (83.3)	1.01 (0.67-1.51)		**15**	1 (6.7)	0.60 (0.05-7.56)		**5**	2 (40.0)	2.51 (0.34-18.53)	
200-350	**45**	26 (57.8)	0.93 (0.65-1.33)		**46**	37 (80.4)	0.99 (0.82-1.19)		**40**	1 (2.5)	0.30 (0.03-3.16)		**46**	18 (39.1)	**2.87 (1.15-7.17)**	
351-500	**42**	24 (57.1)	0.97 (0.68-1.38)		**70**	60 (85.7)	1.07 (0.94-1.23)		**38**	0 (0.0)	-		**67**	14 (20.9)	1.21 (0.50-2.91)	
>500	**52**	31 (59.6)	1		**87**	71 (81.6)	1		**49**	4 (8.2)	1		**80**	16 (20.0)	1	

Adjusted Prevalence Ratio (aPR): [1]Model1: In BF, associations with HR-HPV were adjusted for alcohol use, marital status, age at first pregnancy and cervicitis; and in SA, associations with HR-HPV were adjusted for age, smoking, injectable contraception, condom use, vaginal cleansing, genital warts, bacterial vaginosis (BV), infection with *Chlamydia trachomatis* and *Trichomonas vaginalis*; [2]Model 2: same as Model 1 with additional adjustment for CD4+ count ; Adjusted Odds Ratio (aOR): [3]In BF, associations with CIN2+ were adjusted for age, BV and cervical ectopy; and in SA, associations with CIN2+ were adjusted for age at first pregnancy, injectable contraception and number of lifetime sex partners; [4]Model 2: same as Model 1 with additional adjustment for CD4+ ; [§]CD4+ count was unavailable for 1 participant on ART in BF; [†]HIV-1 PVL data was unavailable for 29 ART users in BF and 4 in SA; [‡]Data on self-reported adherence was unavailable for 24 participants in BF and 4 in SA

Table 4. Effect of HIV related factors on HR-HPV persistence, using infections as unit of measure

	Burkina Faso[1] N=404				South Africa[2] N=598			
	N	n (%)	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)	N	n (%)	Model 1 aOR (95% CI)	Model 2 aOR (95% CI)
Baseline CD4+ count (cells/mm3)								
<200	**55**	30 (54.6)	**2.01 (1.20-3.37)**	-	**39**	11 (28.2)	0.91 (0.28-2.92)	-
200-350	**86**	39 (45.4)	1.10 (0.62-1.96)	-	**148**	47 (31.8)	1.20 (0.88-1.64)	-
351-500	**127**	51 (40.2)	1.11 (0.75-1.66)	-	**189**	63 (33.3)	1.32 (0.85-2.06)	-
>500	**136**	50 (36.8)	1.00	-	**222**	60 (27.0)	1.00	-
ART status at baseline								
ART >2 years	**170**	64 (37.7)	1.00	1.00	**200**	49 (24.5)	1.00	1.00
ART ≤2 years	**123**	41 (33.3)	0.83 (0.54-1.29)	0.75 (0.43-1.31)	**162**	57 (35.2)	**1.75 (1.16-2.65)**	**1.78 (1.11-2.86)**
ART-naive	**111**	65 (58.6)	**2.05 (1.35-3.13)**	**1.89 (1.26-2.83)**	**236**	75 (31.8)	**1.68 (1.02-2.79)**	1.64 (0.98-2.74)
Among ART users[§] :								
HIV-1 viral suppression[*]								
<1000 copies/ml	**244**	82 (33.6)	1.00	1.00	**294**	73 (24.8)	1.00	1.00
≥1000 copies/ml	**32**	13 (40.6)	1.18 (0.70-2.01)	0.88 (0.43-1.83)	**67**	33 (49.3)	**2.76 (1.50-5.11)**	**2.87 (1.63-5.05)**
HIV viral detection[*]								
≤40 copies/ml	**205**	63 (30.7)	1.00	1.00	**124**	32 (25.8)	1.00	1.00
>40 copies/ml	**71**	32 (45.1)	**1.85 (1.38-2.48)**	**1.68 (1.22-2.32)**	**237**	74 (31.2)	1.18 (0.53-2.63)	1.15 (0.53-2.49)
Baseline CD4+ count (cells/mm^3)								
<200	**34**	16 (47.1)	**1.85 (1.15-2.96)**		**34**	9 (26.5)	0.80 (0.25-2.52)	
200-350	**56**	23 (41.1)	1.29 (0.72-2.31)		**103**	28 (27.2)	1.02 (0.68-1.51)	
351-500	**93**	30 (32.3)	0.92 (0.62-1.35)		**103**	35 (34.0)	1.47 (0.84-2.55)	
>500	**110**	36 (32.7)	1.00		**122**	34 (27.9)	1.00	
Stable high CD4+ (≥500 cells/mm^3)								
No	**196**	75 (38.3)	1.37 (0.93-2.00)		**298**	88 (29.5)	1.04 (0.52-2.07)	
Yes	**97**	30 (30.9)	1.00		**64**	18 (28.1)	1.00	
Among ART-naïve:								
Baseline CD4+ count (cells/mm^3)[†]								
<200	**21**	14 (66.7)	1.30 (0.36-4.76)		**5**	2 (40.0)	3.42 (0.57-20.66)	
200-350	**30**	16 (53.3)	0.79 (0.26-2.41)		**45**	19 (42.2)	1.46 (0.79-2.73)	
351-500	**34**	21 (61.8)	1.43 (0.46-4.44)		**86**	28 (32.6)	1.07 (0.45-2.56)	
>500	**26**	14 (53.9)	1.00		**100**	26 (26.0)	1.00	
Stable high CD4+ (≥500 cells/mm^3)[‡]								
No	**53**	34 (64.2)	1.36 (0.43-4.31)		**160**	53 (33.1)	2.15 (0.94-4.89)	
Yes	**20**	9 (45.0)	1.00		**42**	7 (16.7)	1.00	

Adjusted Odds Ratio (aOR) using generalised estimating equation: [1]In BF, associations with HR-HPV were adjusted for alcohol use , marital status, age at first pregnancy and cervicitis ; [2]In SA, associations with HR-HPV were adjusted for age, smoking, injectable contraception, condom use, vaginal cleansing, genital warts, bacterial vaginosis, *Chlamydia trachomatis* and *Trichomonas vaginalis*; [§]ART use was defined as being on ART at both baseline and endline; [*]Baseline HIV-1 PVL data was unavailable for 12 participants in BF (representing 17 infections) and 1 in SA (representing 1 infection); [†]Baseline CD4+ among participants who were ART-naïve at baseline [‡] ART-naïve participants were defined as being ART-naive at both baseline and endline.