

Sustained Viral Suppression and Higher CD4⁺ T-Cell Count Reduces the Risk of Persistent Cervical High-Risk Human Papillomavirus Infection in HIV-Positive Women

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Background. Studies analyzing the impact of combination antiretroviral therapy (cART) on cervical infection with high-risk human papillomavirus (HR-HPV) have generated conflicting results. We assessed the long-term impact of cART on persistent cervical HR-HPV infection in a very large cohort of 652 women who underwent follow-up of HIV infection for a median duration of 104 months.

Methods. Prospective cohort of HIV-infected women undergoing HIV infection follow-up who had HR-HPV screening and cytology by Papanicolaou smear performed yearly between 2002 and 2011.

Results. At baseline, the median age was 38 years, the race/ethnic origin was sub-Saharan Africa for 84%, the median CD4⁺ T-cell count was 426 cells/ μ L, 79% were receiving cART, and the HR-HPV prevalence was 43%. The median interval of having had an HIV load of <50 copies/mL was 40.6 months at the time of a HR-HPV-negative test result, compared with 17 months at the time of a HR-HPV-positive test result ($P < .0001$, by univariate analysis). The median interval of having had a CD4⁺ T-cell count of >500 cells/ μ L was 18.4 months at the time of a HR-HPV-negative test result, compared with 4.45 months at the time of a HR-HPV-positive test result ($P < .0001$). In multivariate analysis, having had an HIV load of <50 copies/mL for >40 months (odds ratio [OR], 0.81; 95% confidence interval [CI], .76–.86; $P < .0001$) and having had a CD4⁺ T-cell count of >500 cells/ μ L for >18 months (OR, 0.88; 95% CI, .82–.94; $P = .0002$) were associated with a significantly decreased risk of HR-HPV infection.

Conclusion. Sustained HIV suppression for >40 months and a sustained CD4⁺ T-cell count of >500 cells/ μ L for >18 months are independently and significantly associated with a decreased risk of persistent cervical HR-HPV infection.

Keywords. HPV; HIV; cervix; women; Sustained undetectable viral load; CD4 count; Immune reconstitution; prevalence; HPV Clearance; HPV Persistence.

Persistent infection with oncogenic high-risk human papillomavirus (HR-HPV), which induces cervical cancer, is more prevalent among human immunodeficiency virus

(HIV)-positive women. In these women, progressive immunodeficiency and higher plasma HIV load significantly increase the rate of HR-HPV carriage and worsen its evolution, leading more frequently to high-grade cervical squamous intraepithelial lesions (HSILs) and invasive cancer [1–4]. Although these relationships have been clearly demonstrated, studies analyzing the effect of combination antiretroviral therapy (cART) on HR-HPV infection have generated conflicting results. Four studies could not find a beneficial impact of cART on HR-HPV infection, but they were limited by small sample sizes, short-term follow-up, and lack of evaluation of cART adherence and efficacy on HIV

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load [5–8]. In contrast, 2 other studies found a significant decrease in HR-HPV prevalence in study subjects 2 years after starting cART [9, 10]. In contrast with decreasing incidences of other opportunistic infections, the scaling-up of cART has been associated with a stable incidence of HPV-induced cervical cancer and a markedly increased incidence of anal cancer [11, 12]. A cumulative HPV exposure secondary to a longer survival duration in cART-treated patients with HIV infection is the leading hypothesis for this observation. However, the absence of a decline in the incidence of HPV-induced cancers with cART scale-up might be due to more complex interactions between duration and level of both immunodeficiency and immune reconstitution, as discussed in a recent editorial by Palefsky [13].

As persistent infection with HR-HPV is the first step before the occurrence of high-grade squamous intraepithelial cervical lesions and invasive cervical cancer [14], there is a need to better understand the relationship between HIV therapy and cervical HR-HPV infection. Our present study assessed the long-term impact of cART on HR-HPV infection in a large cohort of HIV-infected women by evaluating the association between the rate of cervical HR-HPV infection and the time spent in different CD4⁺ T-cell count strata and the time spent with an undetectable HIV load.

METHODS

Since 2002, an ongoing prospective program of screening and follow-up of HR-HPV infection has been systematically offered to all women undergoing follow-up for HIV-1 infection in our AIDS reference center in Saint-Pierre University Hospital (Brussels, Belgium). Women are seen by a dedicated gynecologist within the AIDS reference center and are then followed every year or, if they have complaints or abnormal smear results, more often. At the first and subsequent visits, cytology by Papanicolaou smear (according to the Bethesda Classification) and a HR-HPV screen are performed on a liquid-based sample taken with a cytological brush (ThinPrep and SurePath). HR-HPV (genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68) are detected by Hybrid Capture (hc2 High-Risk HPV DNA Test, Digene, United States). In case of abnormal cytology findings (defined as squamous intraepithelial lesions of any grade or atypical squamous cells of undetermined significance), women undergo colposcopy and cervical biopsy. Women with previous hysterectomy, conization, and/or biopsy-confirmed HSILs or cervical cancer were not included in the cohort as their cervix could not be considered as intact anymore and the natural history of HR-HPV infection could be altered. Women who developed HSIL or cervical cancer or had hysterectomy after being included in the screening program were censored at the time of the event.

Women were consecutively enrolled in the HR-HPV screening program (55 women were enrolled in 2002, 37 in 2003, 42 in 2004, 48 in 2005, 82 in 2006, 67 in 2007, 81 in 2008, 125 in 2009, and 115 between 2010 and February 2011). A prospective database collected all results (HR-HPV positivity, Papanicolaou smear findings, and biopsy results), as well as the following surrogate markers of HIV infection retrieved from the preexisting Saint-Pierre HIV Cohort database: HIV acquisition risk factor; race/ethnic origin; AIDS stage, according to the 1993 Centers for Disease Control and Prevention (CDC) classification; duration of HIV follow-up; CD4⁺ T-cell count (current and nadir); current cART use (yes or no); median duration of cART; HIV load; smoking status; and previous pregnancies. The Saint-Pierre HIV Cohort includes and follows prospectively all patients who have attended our AIDS reference center since 1983 and has been described in details previously [15]; data are collected at each consultation every 3–4 months.

At time of enrollment in the HR-HPV screening program, most of the women had been already followed in the Saint-Pierre HIV Cohort for several years. After inclusion in the HR-HPV program, they continued to be followed prospectively in the HIV cohort. Thus, prospective data on HIV infection and follow-up were available for a prolonged period before and after inclusion in the HR-HPV screening program.

The screening program and the data collection were both approved by the Ethics Committee of Saint-Pierre University Hospital, Brussels.

HR-HPV prevalence was calculated as the proportion of women with HR-HPV detected at the first screen; the cumulative prevalence was calculated as the proportion of women with at least 1 HR-HPV-positive test result during the study period (including both first and follow-up screenings). To calculate the HR-HPV incidence, we considered all women whose initial sample tested negative for HR-HPV and who had at least 1 additional sample tested.

The duration of sustained HIV undetectability was calculated as the interval from the midpoint between the date of the first undetectable HIV load and the first preceding date on which the HIV load was detectable to the midpoint between the date of the last undetectable HIV load and either the date of the first subsequent detectable HIV load or the date of the HR-HPV screening considered for the analysis. If a patient had 1 or several detectable HIV load measurement(s) alternating with an undetectable HIV load, we added all of the periods during which the HIV load was undetectable.

The time spent in each CD4⁺ T-cell count stratum was calculated the same way as the duration of sustained HIV undetectability was calculated.

First HR-HPV Screening

We compared women who tested positive for HR-HPV at baseline to women with a negative test result at baseline by

univariate analysis (the χ^2 or Fisher exact tests were used for categorical data, and the Kruskal-Wallis test was used for continuous data) and by multivariate analysis (logistic regression).

Clearance Versus Persistence

We analyzed clearance and persistence of HR-HPV infection in the follow-up samples by using conservative definitions previously used in other studies [8], in which clearance was defined as a HR-HPV-positive test result followed by 2 consecutive negative test results any time during follow-up. Among women without clearance, persistence was defined as a HR-HPV-positive test result followed by at least 2 consecutive test results that were not both negative. If a woman had several sequences of clearance, persistence, or both, only the first sequence was taken into account. The estimated date of clearance or persistence was defined as the midpoint between the dates of the first and second tests in the sequences described above. Comparison was made between the 2 groups at the time of clearance or persistence by univariate analysis (the χ^2 or Fisher exact tests were used for categorical data, and the Kruskal-Wallis test was used for continuous data) and by multivariate analysis (logistic regression).

HR-HPV at Any Time During Study

Because of the high heterogeneity of the sequences, HR-HPV in most of the patients did not fulfill the conservative definition of clearance or persistence. Another drawback of using specific cutoffs such as clearance and persistence (both of which, by definition, happen at a precise moment) is that the impact of progressive immune restoration—a continuous process—could not be taken into account. To avoid these 2 pitfalls, we took all consecutive HPV tests into account, including all baseline and follow-up results. We evaluated the predictive factors of HR-HPV carriage at any time during the study by univariate analysis (the χ^2 or Fisher exact tests were used for categorical data, and the Kruskal-Wallis test was used for continuous data) and multivariate analysis performed by marginal logistic test regression.

RESULTS

From January 2002 to February 2011, 825 women had at least 1 cervical screen for HPV. Women with previous HSIL or cervical cancer confirmed by biopsy ($n = 141$) or a hysterectomy for nononcologic reasons ($n = 32$) were excluded, leaving 652 patients for the final analysis. Women who developed HSIL or cervical cancer ($n = 29$) or had a nononcologic hysterectomy ($n = 5$) after being included in the screening program were censored at the time of the event.

The cohort of 652 women consisted mainly of women whose ethnic origin was sub-Saharan Africa (531 [84%]), who acquired HIV via heterosexual sex (613 [94%]), and who did not

smoke (471 [72%]). At the time of the first HR-HPV screen, the median age was 38 years (interquartile range [IQR], 31–45 years), the median CD4⁺ T-cell count was 426 cells/ μ L (IQR, 302–601 cells/ μ L), and the median nadir CD4⁺ T-cell count was 222 cells/ μ L (IQR, 120–339 cells/ μ L), with a nadir of <100 cells/ μ L in 135 women. One hundred four women (16%) received a diagnosis of CDC stage C AIDS in the past, and the median duration of HIV follow-up was 65.5 months (range, 0–310 months). A total of 515 women (79%) were receiving cART (median duration, 23 months), and 366 (56%) had an undetectable HIV load, defined as an HIV load of <50 copies/mL (range for the whole cohort at the first HR-HPV screen, <50–555 000 copies/mL).

First HR-HPV Screen

The prevalence of HR-HPV infection at the first screen was 42.8% (95% confidence interval [CI], 38.9%–46.7%). The prevalence decreased significantly with age, with values of 65% for women aged <30 years ($n = 127$), 46% for those aged 30–39 years ($n = 239$), 29% for those aged 40–49 years ($n = 201$), and 32% for those aged >49 years ($n = 85$; $P < .0001$, by the χ^2 test). The prevalence of HR-HPV infection also decreased significantly with increasing CD4⁺ T-cell count, with values of 63% for counts of <200 cells/ μ L ($n = 67$), 53% for counts of 200–349 cells/ μ L ($n = 148$), 43% for counts of 350–499 cells/ μ L ($n = 181$), and 28% for counts of >499 cells/ μ L ($n = 226$; $P < .0001$, by the χ^2 test).

Characteristics of the patients, stratified by baseline HR-HPV test result, are described in Table 1. In univariate analysis, women with HR-HPV infection were statistically significantly younger ($P < .0001$), had a lower median CD4⁺ T-cell count at the time of HR-HPV screening ($P < .0001$), and were more likely to have had more-advanced CDC stage AIDS ($P = .004$) and a lower nadir CD4⁺ T-cell count ($P = .03$ for a CD4⁺ T-cell count of <350 cells/ μ L and $P = .007$ for a CD4⁺ T-cell count of <500 cells/ μ L). Women with a negative HR-HPV test result at baseline were more likely to have undergone HIV infection follow-up for >5 years ($P = .0002$) and to have received cART for >2 years ($P < .0001$). The proportion of women in whom the cumulative duration of HIV undetectability was >2 years was significantly higher in the HR-HPV-negative group ($P < .0001$ for HIV loads of <400 and <50 copies/mL). There was no statistically significant difference in terms of race/ethnic origin, HIV acquisition route, smoking status, or previous pregnancy.

In multivariate analysis (Table 2), age of <35 years, nadir CD4⁺ T-cell count of <500 cells/ μ L, and diagnosis of CDC stage B or C AIDS were each significantly associated with an increased odds of being HR-HPV positive at the first screen. Women who were treated with cART for ≥ 24 months or who had had an undetectable HIV load (ie, an HIV load of <50

Table 1. Characteristics of 652 Women, According to Result of Baseline Screening for High-Risk Human Papillomavirus (HR-HPV)

Characteristic	HR-HPV Positive (n = 279)	HR-HPV Negative (n = 373)	<i>P</i> ^a
Race/ethnic origin			
Sub-Saharan Africa	233 (84)	298 (83)	.31
White	38 (14)	61 (17)	
HIV transmission route, women, %			
Heterosexual sex	98	99	.66
Injection drug use	2	1	
CDC stage B or C AIDS	94 (34)	83 (22)	.0012
Age			
Overall, median, y	34	40	<.0001
<35 y	144 (52)	101 (27)	<.0001
Nonsmoker	197 (71)	274 (73)	.42
At least 1 previous pregnancy	69 (25)	104 (28)	.36
CD4⁺ T-cell count			
Overall, cells/μL, median	359	474	<.0001
<200 cells/μL	17	6	<.0001 ^b
<350 cells/μL	47	26	<.0001 ^c
Nadir			
Overall, cells/μL, median	215	233	.0012
<200 cells/μL	44	41	.05104 ^b
<350 cells/μL	81	73	.0326 ^c
<500 cells/μL	95	90	.0071 ^d
Duration of HIV follow-up			
Overall, mo, median	47	77	<.0001
≥5 y	44	59	.0002
Current cART use			
Overall, women, %	76	82	.0456
Duration			<.0001
Overall, mo, median	12	37	
≥24 mo	155 (56)	283 (76)	<.0001
Duration of viral suppression to <400 copies/mL			
Overall, mo, median	9	28	<.0001
≥24 mo	77 (29)	199 (54)	<.0001
Duration of viral suppression to <50 copies/mL			
Overall, mo, median	6	23	<.0001
≥24 mo	50 (19)	178 (49)	<.0001

Data are no. (%) of women, unless otherwise indicated. Univariate analysis was performed by means of χ^2 and Kruskal-Wallis tests.

Abbreviations: cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; mo, months; y, year.

^a HR-HPV-positive women vs HR-HPV-negative women, unless otherwise indicated.

^b Women with a CD4⁺ T-cell count of <200 cells/μL vs those with a CD4⁺ T-cell count of ≥200 cells/μL.

^c Women with a CD4⁺ T-cell count of <350 cells/μL vs those with a CD4⁺ T-cell count of ≥350 cells/μL.

^d Women with a CD4⁺ T-cell count of <500 cells/μL vs those with a CD4⁺ T-cell count of ≥500 cells/μL.

Table 2. Multivariate Logistic Regression Analysis of Factors Predictive for High-Risk Human Papillomavirus (HR-HPV) Detection at Baseline

Factor	OR (95% CI)	<i>P</i>
Age <35 y	2.52 (1.69–3.75)	<.0001
Median CD4 ⁺ T-cell count <200 cells/μL	1.82 (.78–3.39)	.0582
Nadir CD4 ⁺ T-cell count <500 cells/μL	3.31 (1.51–7.24)	.0027
CDC stage B or C AIDS	2.5 (1.62–3.88)	<.0001
HIV follow-up for >5 y	0.76 (.48–1.21)	.254
Current cART use	0.72 (.41–1.27)	.1907
cART use for ≥2 y	0.6 (.37–.99)	.0471
HIV load <50 copies/mL for ≥2 y	0.28 (.17–.49)	<.0001

Abbreviations: cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HIV, human immunodeficiency virus; OR, odd ratio; y, year.

copies/mL) for ≥24 months had a decreased odds of HR-HPV carriage at baseline (*P* < .04 and *P* < .0001, respectively).

Follow-up HR-HPV Detection

HR-HPV testing was performed once in 304 women, twice in 155, 3 times in 100, and ≥4 times in 93 women. The median number of HPV tests per woman was 2 (range, 1–11 tests; 10th–90th percentiles, 1–4 tests), with a median interval of 15.5 months (IQR, 9–28 months) between 2 consecutive tests. The median duration between the first and the last HR-HPV screen in the study was 38 months (IQR, 21–62 months). At time of the last HR-HPV screen, women had been undergone HIV infection follow-up for a median duration of 103 months (IQR, 67–152 months). The cumulative prevalence of HR-HPV during the whole program was 51% (95% CI, 47%–55%). Among the 165 patients for whom the first screen was negative for HR-HPV and was followed by at least 1 test, 54 subsequently tested positive for HR-HPV during the 4824 patient-months of follow-up, for an incidence rate of 13.4 cases per 100 woman-years (95% CI, 6.4–20.9).

Clearance Versus Persistence

We could apply the conservative definition of HR-HPV clearance or persistence to 140 women: clearance was found in 63 women and persistence in 77 women. In univariate analysis, women with clearance were more likely to have had a median HIV infection follow-up duration of ≥5 years (63% vs 45%; *P* = .033) and to have an undetectable HIV load for a longer period (HIV load < 400 copies/mL, 32 vs 19 months [*P* = .01]; HIV load < 50 copies/mL, 27.5 vs 16.5 months [*P* = .009]). The 2 groups were similar at the time of clearance or persistence in terms of age (37 years), race/ethnic origin (82% had sub-Saharan Africa ethnic origin), smoking status (29% were smokers), previous pregnancy (26%), previous CDC C AIDS (20%), cART duration of ≥2 years (83% for women who

Table 3. Univariate Analysis of Factors Predictive of High-Risk Human Papillomavirus (HR-HPV) Detection During the Study

Factor	At time of HR-HPV-Positive Screen	At time of HR-HPV-Negative Screen	<i>P</i>
Age, women, %			<.0001
<30 y	65	35	
30–40 y	46	54	
40–50 y	35	65	
>50 y	40	60	
Duration of CD4 ⁺ T-cell count, mo, median			
<200 cells/ μ L	0	0	NS
200–350 cells/ μ L	10.4	9.53	NS
350–500 cells/ μ L	12.3	16	.0002
>500 cells/ μ L	4.45	18.4	<.0001
Duration of HIV load <50 copies/mL, mo, median	17	40.6	<.0001

Analysis was performed by means of χ^2 and Wilcoxon tests.

Abbreviations: HIV, human immunodeficiency virus; mo, month; NS, not significant.

cleared HR-HPV vs 70% for those who did not; $P = .09$), median CD4⁺ T-cell count (463 cells/ μ L for women who cleared HR-HPV vs 462 cells/ μ L for those who did not; $P =$ not significant), and nadir CD4⁺ T-cell count (202 cells/ μ L for women who cleared HR-HPV vs 197 cells/ μ L for those who did not; $P =$ not significant). In multivariate analysis, women with an undetectable HIV load for ≥ 24 months had an increased chance of clearing HR-HPV (odds ratio [OR], 1.018; 95% CI, 1.001–1.035; $P < .039$ for HIV loads of <400 and <50 copies/mL).

HR-HPV at Any Time During Study

We evaluated the predictive factors for HR-HPV carriage at any time during the study by taking into account all consecutive HPV tests, including baseline and follow-up results. In univariate analysis (Table 3), at the time of a HR-HPV-negative test result, women were older ($P < .0001$), had spent a longer median interval in the higher CD4⁺ T-cell count strata (16 vs 12.3 months with a CD4⁺ T-cell count of 350–500 cells/ μ L [$P = .002$] and 18.4 vs 4.5 months with a CD4⁺ T-cell count of >500 cells/ μ L [$P < .0001$]), and had an HIV load of <50 copies/mL for a longer duration (40.6 vs 17 months; $P < .0001$), compared with women with HR-HPV.

In multivariate analysis, women aged <30 years had an increased risk of a HR-HPV-positive test result any time during the study (OR, 3.13; 95% CI, 1.8–5.6; $P < .0001$ [OR = 1 for age >50 years]), but having a CD4⁺ T-cell count of >500 cells/ μ L for >18 months was associated with a significantly decreased risk (OR, 0.88; 95% CI, .82–.94; $P = .0002$). Women with an HIV load of <50 copies/mL for >40 months had also a

significantly decreased risk of testing positive for HR-HPV (OR, 0.81; 95% CI, .76–.86; $P < .0001$).

DISCUSSION

In this large cohort of 652 women who underwent follow-up for HIV infection for several years and had a high prevalence of HR-HPV coinfection, we found that the risk of HR-HPV carriage significantly decreased in those with sustained immunological reconstitution (ie, a CD4⁺ T-cell count of >500 cells/ μ L for >18 months) and long-lasting HIV suppression (<50 copies/mL for >40 months). These results were reproducible and highly significant, whether we considered only the first HR-HPV screen or persistent and cleared infections, defined according to a conservative definition, or the risk of HR-HPV carriage at any time during follow-up.

Our results accord with those of 2 other studies. The ACTG A5029 trial followed 146 women who started cART prospectively for 2 years, with efficacy assessed by repeated measurement of the CD4⁺ T-cell count (which increased from 238 to 426 cells/ μ L) and the HIV load (63% had an HIV load of <50 copies/mL at study end) [9]; HR-HPV detection decreased from 62% to 39% after 2 years, and this was significantly associated with a longer follow-up duration. In another study, Minkoff et al found a significant decline in the HR-HPV prevalence 2.5 years after initiation of cART in 144 women who reported to be adherent to their therapy [10]; in contrast, the HR-HPV prevalence remained stable in the 142 nonadherent patients. However, the decrease in prevalence among women receiving an effective cART regimen, as defined by repeatedly undetectable HIV loads, was only marginally significant ($P = .06$), suggesting that 2.5 years of cART is too short of an interval to obtain significant HR-HPV clearance. Indeed, our results show that it could take >3 years of undetectable HIV loads and >1.5 years of CD4⁺ T-cell counts of >500 cells/ μ L to obtain a clearance of HR-HPV.

Three other studies found that cART did not have a beneficial effect against cervical HR-HPV infection. In contrast to our study, these cohorts included fewer patients and had a shorter maximum follow-up duration of 2 years [5–7]. In these studies, which included patients who were treated in the 1990s, the lack of demonstration of cART's efficacy against HR-HPV infection could be due to cART's suboptimal efficacy against HIV itself. Indeed, the older antiviral regimens included numerous pills to be taken several times per day and had higher rates of intolerance, such as gastrointestinal side effects. Because these studies did not provide information on adherence or on HIV load, their findings on the efficacy of cART could be questioned. In the HER study [7], information on cART use was assessed from patients only by self-report. A subsequent report from the same cohort confirmed poor cART adherence (64% during the first month, then 45% after 6 months) and the likely poor

virological response [16]. In a recent study, there was no beneficial effect on HR-HPV clearance in 100 patients: although the CD4⁺ T-cell count increased from 471 to 525 cells/ μ L, the follow-up duration was only 14 months after starting cART [8].

In contrast, we assessed the efficacy of cART by measuring both the time spent with an undetectable HIV load and the subsequent immune restoration, calculated by the cumulative time spent in each CD4⁺ T-cell count stratum. We could provide these data during the study period of 38 months, but we also had a reliable prospective database with data on surrogate markers available for all enrolled patients for a median duration of 66 months before they entered the HPV study, allowing assessment of the immune reconstitution during cART over a long period.

The positive impact of long-term HIV control on HR-HPV infection is biologically plausible: a higher HIV load is associated with a higher prevalence of HR-HPV and is independent of the CD4⁺ T-cell count [2–4, 17]. HIV viremia has also been shown to act as an independent risk factor for other opportunistic infections, such as *Pneumocystis pneumonia* or refractory candidiasis [18, 19]. This may reflect that an uncontrolled HIV load is responsible not only for CD4⁺ T-cell destruction but also for decreasing other immune functions not measurable in routine practice and that are correlated with HR-HPV infection control, such as cytokine production. Indeed, cytokine responses to HPV infection are altered in cervical cells of HIV-positive women [20]. Contrasting with most opportunistic pathogens, HR-HPV leads to cancer also in immunocompetent persons, so even subtle changes in immune function might be responsible for higher HR-HPV prevalences in HIV-positive patients. This has been demonstrated in HIV-positive adolescents with CD4⁺ T-cell counts of >500 cells/ μ L who had a significantly higher rate of persistent HR-HPV infection than HIV-negative controls [21].

Another recent study [22] found that the risk of newly detected HR-HPV increased by 2.5–5 times 3–6 months after acquiring HIV infection, confirming findings from animal models, in which HIV induced severe depletion of genital tract immunity immediately during acute infection [23].

As a consequence, prolonged immune restoration induced by an efficient cART regimen would be needed before any improvement on HR-HPV infection could be measured. The significant benefit of an efficient cART regimen against HR-HPV infection demonstrated in our cohort, in which the median duration of HIV infection follow-up is >8 years, sustains this hypothesis. Persistent HR-HPV infection precedes invasive cancer by 10–15 years, which might explain why the incidence of cervical cancer has not yet decreased in the cART era.

Our study has several limitations. First, we used a hybrid capture technique to detect HR-HPV infection. Because the sensitivity of this technique is inferior to that of PCR techniques, our prevalence and incidence rates might be underestimated.

However, the specificity of hybrid capture is higher than that of PCR in HIV-positive women [24, 25], and the genotypes detected with hybrid capture have been recently confirmed as high risk by the International Agency for Research on Cancer [26]. We could not generate results according to the different HR-HPV genotypes. However, because HIV-positive women are more likely to carry multiple HR-HPV genotypes concomitantly [27], the studies that used PCR had to aggregate the results according to “high-risk” or “low-risk” types to reach statistical significance, owing to small numbers of patients per genotype [6, 9, 10]. Second, the median interval between 2 screenings was 15 months, so transient HPV infection could have been missed (ie, some women might have acquired and then lost HR-HPV between visits), but because we have focused on persistent infection defined as lasting >6 to 12 months, transient infection would not impact our results.

In conclusion, sustained HIV suppression for >40 months and a CD4⁺ T-cell count of >500 cells/ μ L for >18 months are independently and significantly associated with HR-HPV control and a lower risk of persistent cervical HR-HPV infection. In women, initiation of cART early in the course of HIV infection, to achieve a high CD4⁺ T-cell count and sustained undetectable viral load, could reduce the incidence of HR-HPV infection and, subsequently, the incidences of induced cervical dysplasia and cancer. This strategy deserves further study.

Notes

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