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Oral Lopinavir Use and Human Papillomavirus Infection in HIV-positive Women

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Keywords

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Introduction

Invasive cervical cancer (ICC) is the third most common female malignancy and fourth most common cause of cancer death in women globally[1]. The risk of ICC is several-fold higher in HIV-positive women than in HIV-negative women, as are the prevalence[2–5], incidence, and persistence of oncogenic human papillomavirus (oncHPV)[6–14], the infectious cause of most ICC. Although use of effective highly-active antiretroviral therapy (HAART) has been associated with reduced oncHPV prevalence and incidence[15] and increased regression of cervical lesions[16–19], the overall incidence of ICC has not decreased in HIV-positive women during the HAART era. By increasing survival, HAART may increase lifetime oncHPV infections, allowing accumulation of somatic mutations and epigenetic changes necessary for oncogenesis. Currently, no anti-viral medications are clinically approved to treat cervical HPV infections.

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In vitro studies have shown that lopinavir (LPV), an HIV-1 protease inhibitor (PI) used in some HAART regimens, may have activity against oncHPV through inhibition of viral oncogene E6[20, 21]. Most recently, an early phase clinical trial conducted in Nairobi, Kenya studied topical application of LPV to the cervix; preliminary results showed that 21 of 23 women initially diagnosed with high-grade disease returned to normal on subsequent Papanicolaou (Pap) smears and showed visible regression of cervical lesions[22].

We therefore assessed the hypothesis that oral LPV use may be associated with decreased prevalence and increased clearance of oncHPV compared to other antiretroviral (ARV) regimens.

Methods

Study population and specimens

Specimens and data were obtained from the Women's Interagency HIV Study (WIHS), a prospective cohort of 2791 HIV-positive and 975 HIV-negative women either enrolled during 1994–1995 or 2001–2002 at six clinical sites: Bronx, NY; Brooklyn, NY; Chicago, IL; Los Angeles, CA; San Francisco, CA; and Washington, DC. WIHS data collection methods have been described previously[23]. Briefly, during each semiannual visit, participants underwent physical and gynecological examination, Pap tests, and cervicovaginal lavage fluid (CVL) collection[24].

The following inclusion criteria were used: HIV-positive, attended ≥ two WIHS study visits, receiving HAART during ≥ one visit, and ≥ one adequate HPV test at any visit over the ensuing 5 year period. Study visits during which the participant was receiving HAART with an undetectable HIV viral load were included in the oncHPV prevalence and clearance analyses; this minimized concerns that results might be affected by use of an inadequate HAART regimen or poor adherence.

Detection of Oncogenic HPV DNA

HPV DNA testing was performed in CVLs using a well-established MY09/MY11 PCR, as previously described[11]. Oncogenic HPV types, defined by the International Association for Research on Cancer (IARC), included HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68[25].

Statistical analyses

The baseline visit was defined as the first visit for which the subject contributed data, i.e., following widespread LPV availability and its use in WIHS.

Descriptive statistics compared baseline characteristics of women who ever received LPV versus women who never received LPV either before or during their enrollment in WIHS using chi-squared tests for categorical variables, two-sided t-tests for normally distributed continuous variables, and Wilcoxon rank sum tests for non-normally distributed continuous variables.

Generalized estimating equation (GEE) methods were used to study the prevalence and clearance of oncHPV, comparing women using LPV-based HAART, other PI based HAART, and non-PI based HAART. As previously described[26], GEE accounts for multiple observations per subject, including multiple individual HPV types at each visit, multiple follow-up visits, and changing HAART regimens over time, while accounting for within-individual correlations between these observations. A subject can therefore contribute data to more than one exposure group over time. HPV clearance was defined on a type-specific basis using two commonly employed definitions: (i) the first negative result or (ii) two sequential negative results. Results were similar using both definitions, and we present results based on the latter, more conservative definition. Time to clearance was not possible given the limited data after excluding visits where women had detectable HIV viral load. Variables considered to be clinically relevant based on prior literature were included in the multivariate model regardless of statistical significance, including age, race, CD4 count, smoking status, number of male sexual partners, and pregnancy. To adjust for possible selection bias in LPV use, multivariate analyses were repeated using propensity score analysis[27]. Specifically, the propensity for using LPV at each visit was estimated using a logistic regression model with covariates and was included in the model on HPV prevalence and clearance as a linear and/or polynomial variable. Women who received cervical treatment were censored at the visit prior to treatment.

All analyses were performed using SAS® 9.3 (SAS Institute, Cary, NC) software with an alpha level of 0.05 using two-sided statistical tests.

Results

Compared to women who never used LPV (n=1058), women who had ever used LPV (n=233) were younger (mean age 37.3 versus 38.5 years, p=0.05), had lower median CD4 T-cell counts (CD4 = 298 [interquartile range (IQR): 161–477] versus CD4 = 428 [IQR: 256–626]; p<0.0001), and were less likely to have undetectable HIV RNA levels (57% vs. 75%, p <0.0001). Both groups had similar baseline oncogenic and non-oncogenic HPV infection rates. There were no differences in race/ethnicity, smoking history, number of male partners, condom use, or prior use of other PIs.

We compared oncHPV prevalence and clearance at study visits in virally suppressed participants currently receiving (i) LPV-based HAART, (ii) other-PI based HAART, or (iii) non-PI HAART. Multivariate results are shown in Table 1. The table shows person-visits rather than number of subjects, since subjects could provide data to multiple HAART exposure groups as their regimens changed over time. Lower CD4 count was associated with greater oncHPV prevalence (p<0.0001) and reduced clearance (p=0.02). Age over forty years was associated with reduced oncHPV prevalence (p=0.02) but not increased clearance. There was no significant difference in oncHPV prevalence between LPV-based HAART users and non-PI HAART users: adjusted OR (aOR) 1.41, 95% CI 0.91–2.20; similarly, there was no significant difference in oncHPV clearance between these two groups, whether clearance was defined by a single negative result or two sequential negative results, aOR 0.47 (95% CI 0.21–1.04, p=0.06). Similar results for oncHPV prevalence and clearance were obtained when considering length of use of each HAART regimen (data not shown). In

addition, compared with non-PI users, women using PIs other than LPV did not have significant differences in prevalent oncHPV infection (aOR 1.30, 95% CI 0.96–1.75) or oncHPV clearance (aOR 1.24, 95% CI 0.69–2.21). Lastly, to address the possibility that differences in characteristics between those who did and did not use LPV may have affected our findings, we conducted similar analyses adjusted for propensity scores related to LPV use. However, the relationships between LPV and oncHPV prevalence and clearance were unchanged.

Discussion

Contrary to our hypothesis, we found no evidence that oral LPV use is associated with decreased oncHPV prevalence or increased clearance in cervicovaginal specimens from HIV-positive women. This may be due to lower LPV concentrations in the female genital tract when LPV is used orally rather than topically applied to the cervix[28, 29]. Nonetheless, these findings suggest that use of oral LPV-based HAART is unlikely to reduce the burden of cervical vaginal oncHPV relative to other effective HAART regimens.

It is important to note that the analyses were limited to visits during which the HIV-infected women studied were virally suppressed, reducing the possibility that findings might be due to an inadequate HAART regimen or non-adherence. On the other hand, we found important differences in the characteristics of LPV users and non-users, which we addressed in several ways. Specifically, LPV users were younger, had higher initial HIV-1 viral loads, and were more immunosuppressed than LPV non-users. These differences raised the possibility of "selection by indication"; i.e., women who were sicker may have been preferentially started on LPV compared to other regimens. To address the possibility that selection by indication may have affected our findings, we repeated all analyses, adjusted for propensity scores related to LPV use. The results remained essentially unchanged; albeit, the possibility of residual confounding can never be fully excluded.

Additionally, the data were too limited to conduct analyses stratified by meaningful subgroups, or to conduct time to event analyses for clearance. While we examined clearance with a widely accepted definition of two sequential visits and incorporated multiple longitudinal observations per subject, time to event would have been the preferred approach. Finally, we did not assess LPV drug levels in serum or cervical tissue. Conversely, strengths of this study included a well characterized cohort population, standardized specimen and data collection every 6 months, and central laboratory testing with well established PCR assays.

Overall, our data suggest that use of oral LPV neither reduces HPV prevalence nor increases clearance in HIV-positive women. Selection of HAART regimens should be based on other clinical and patient factors. Whether or not topical LPV is of benefit in treating HPV-associated cervical lesions is not addressed by these data and deserves further study. If effective, topical therapies would be particularly useful in resource-poor settings where burden of disease is high and access to HPV vaccines and colposcopy are limited.

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Table 1

Multivariate Logistic Regression Analysis of oncHPV[a] Prevalence and Clearance

Covariate	oncHPV Prevalence		oncHPV Clearance	
	Person–Visits N (%)	**OR[b] (95% CI[c])**	**Person–Visits N (%)**	**OR (95% CI)**
Non-PI[d] based HAART[e]	1328 (50%)	Ref	140 (45%)	Ref
LPV[f] based HAART	267 (10%)	1.41 (0.91–2.20)	41 (13%)	0.47 (0.21–1.04)
Non-LPV PI based HAART	1056 (40%)	1.30 (0.96–1.75)	133 (42%)	1.24 (0.69–2.21)
CD4 Count				
>500	1462 (56%)	Ref	116 (37%)	Ref
200–500	979 (38%)	2.23 (1.66–3.00)*	158 (51%)	0.53 (0.30–0.93)*
<200	164 (6%)	3.56 (2.43–5.24) *	37 (12%)	0.50 (0.19–1.29)
Age				
<30	350 (13%)	Ref	60 (19%)	Ref
30–39	1029 (39%)	0.72 (0.49–1.08)	123 (39%)	0.55 (0.24–1.27)
40+	1272 (48%)	0.58 (0.38–0.88) *	131 (42%)	0.44 (0.18–1.06)
Race				
Black	1136 (43%)	Ref	162 (52%)	Ref
White	514 (19%)	0.64 (0.41–1.01)	46 (15%)	1.55 (0.65–3.74)
Hispanic	901 (34%)	0.61 (0.43–0.85) *	94 (30%)	1.20 (0.68–2.14)
Other	100 (4%)	0.82 (0.33–2.03)	12 (4%)	1.18 (0.33–4.31)
Smoking				
Never	1028 (39%)	Ref	138 (44%)	Ref
Former	703 (27%)	0.73 (0.50–1.05)	58 (19%)	1.19 (0.54–2.59)
Current	909 (34%)	1.05 (0.75–1.45)	117 (37%)	1.32 (0.73–2.39)
Number male partners in past 6 months				
0	859 (33%)	Ref	82 (26%)	Ref
1+	1764 (67%)	1.10 (0.75–1.63)	229 (74%)	2.32 (0.96–5.60)
Condom Use in past 6 months				
No	1152 (44%)	Ref	118 (38%)	Ref
Yes	1493 (56%)	1.10 (0.79–1.53)	196 (62%)	0.56 (0.26–1.19)
Pregnant at visit				
No	2596 (98%)	Ref	306 (97%)	Ref
Yes	54 (2%)	0.73 (0.35–1.55)	8 (3%)	0.89 (0.21–3.71)

[a] oncHPV = oncogenic human papillomavirus,

[b] OR = odds ratio,

[c] CI = confidence interval,

[d] PI = protease inhibitor,

[e] HAART = highly active antiretroviral therapy,

[f] LPV = lopinavir

* denotes $p < 0.05$