Epidemiology
Open Access

Amirian et al., Epidemiol 2013, 3:4
http://dx.doi.org/10.4172/2161-1165.1000139

Research Article Open Access

Preliminary Findings on the Effects of Interferon-α Treatment on Human Papilloma virus Infection in a Small Pilot Study of HIV and Hepatitis C Virus Co-Infected Men

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Abstract

Human Papilloma Virus (HPV) has been etiologically linked with a number of different cancers. A few older studies have evaluated the effects of Interferon-alpha (IFN-α) treatment on HPV infection and HPV-related dysplasia. However, findings from these studies may not be generalizable to the more recent formulations of IFN-α that are now used to treat Hepatitis C Virus (HCV) infection. The purpose of this small pilot study was to assess whether treatment for HCV by pegylated, rather than standard, IFN-α was associated with the presence of or distribution of the types of HPV found in the oral, penile, and anal regions of HIV and HCV co-infected men. A total of 33 men were enrolled in this pilot study. Of these, 10 were in the IFN-α-exposed group and 23 were in the IFN-α-naïve comparison group. The IFN-α-naïve group had a higher average number of different HPV types present in penile and oral swabs, but not in anal swabs, compared to the treated group. The results of this small pilot study are preliminary. However, our findings have provided some rationale for continuing to explore whether pegylated IFN-α may be a useful adjuvant therapy, or whether it could be combined with other treatment modalities for controlling HPV infection (or disease), specifically of the penis or oral mucosa, among high-risk and HIV-Infected populations.

Keywords: Human papilloma virus; Hepatitis C virus; HIV; Interferon-alpha

Introduction

Approximately one third of the known 120 types of Human Papilloma Virus (HPV) can infect the anogenital region [1-3]. Infection with high-risk HPV types is the main causal factor in cervical cancer etiology, and HPV infections have also been associated with lesions of the anus, penis, vulva, and upper aero-digestive tract [4-7]. Among HIV-infected individuals, the prevalence's of HPV infection in the oral, penile, and anal regions have been reported to be higher compared to the general population [8-12]. Additionally, HIV-infected individuals have been shown to be more likely to be infected with a high-risk HPV type and with multiple HPV types, compared to HIV-negative individuals [9]. Partly attributable to these reasons, HIV-positive individuals have higher risks for anal, oral, and penile cancers [8-10,13-15].

A few older studies have evaluated the effects of Interferon-alpha (IFN-α) treatment on HPV infection and HPV-related dysplasia [16-21]. Findings from these studies were mixed, but most results were based on the use of standard IFN-α therapy and thus, may not be generalizable to the more recent formulations of IFN-α that are now used to treat Hepatitis C virus (HCV) infection. The purpose of this small pilot study was to assess whether treatment for HCV by pegylated, rather than standard, IFN-α was associated with the presence of or distribution of the types of HPV found in the oral, penile, and anal regions of HIV and HCV co-infected men. By examining a small number of high-risk individuals, this study provided further rationale for exploring the possible utility of pegylated IFN-α for prevention of HPV-related disease in high-risk populations.

Materials and Methods

Study population

HIV and HCV co-infected men, at least 18 years of age, undergoing treatment or follow-up for their HCV infection at Thomas Street Health Center, a freestanding HIV-AIDS clinic affiliated with the Harris Health System in Houston, Texas, were recruited by trained study personnel between 2010 and 2011. Eligibility criteria for the treatment-exposed group included having received IFN-α treatment for at least one month just prior to study enrollment. If IFN-α treatment had ended more than two weeks prior to study enrollment, the individual was not considered eligible for the study. For the IFN-naïve group, subjects must never have received IFN-α therapy. A total of 33 men consented to be enrolled in this pilot study. Of these, 10 were in the IFN-α-exposed group and 23 were in the IFN-α-naïve comparison group.

Data collection

At the study visit, participants completed a validated risk factor questionnaire (in English or Spanish) and underwent a standardized external anogenital exam. The questionnaire asked participants to self-report demographics, sexual history, sexually-transmitted infections, and recreational drug use, among other factors. During the anogenital exam, the presence and size of condylomas and/or other genital lesions was noted. Findings were recorded in a systematic fashion per standard clinical protocol. Trained research personnel also collected squamous

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Received August 27, 2013; **Accepted** October 28, 2013; **Published** October 30, 2013

Citation: Amirian ES, Chiao EY, Hill KT, Marquez-Do D, Scheurer ME (2013) Preliminary Findings on the Effects of Interferon-α Treatment on Human Papilloma virus Infection in a Small Pilot Study of HIV and Hepatitis C Virus Co-Infected Men. Epidemiol 3: 139. doi:10.4172/2161-1165.1000139

epithelial samples from the anus, penis, and oral cavity using moisten Dacron swabs according to previously reported methods [22,23].

Trained research personnel conducted standardized medical record review for each participant. The following information was abstracted from each record: age, sexual behaviour history, smoking history, nadir CD4 cell count, most recent CD4 cell count, most recent HIV viral load, HCV type, HCV viral load, and HAART regimen and adherence.

Laboratory assays

The prevalence and types of HPV present in the anal, penile, and oral swabs were determined using the Roche HPV Linear Array (Roche Molecular Systems, Pleasanton, CA), according to the manufacturer's instructions. The array is capable of differentiating between 37 HPV types (HPV-6, -11, -16, -18, -26, -31, -33, -35, -39, -40, -42, -45, -51, -52, -53, -54, -55, -56, -58, -59, -61, -62, -64, -66, -67, -68, -69, -70, -71, -72, -73, -81, -82, -83, -84, -89, IS39). Positive and negative controls were included in each experiment. Laboratory personnel were unaware of the participants' IFN-α treatment status while running the arrays.

Statistical analyses

Demographics and risk factors were summarized using descriptive statistics and compared between treatment groups by Fisher's exact test. Number of HPV types, as well as the presence of high-risk types, was also examined by other potentially relevant covariates, including education and sexual orientation. Due to the pilot nature of this study, multivariable regression analyses were not appropriate.

Results

The distributions of demographic and other factors by treatment group are presented in Table 1. Although there were no statistically

Characteristic	Total (n=33)	Non-IFN Group (n=23)*	IFN-Treated Group (n=10)*	Fisher's Exact P
Education Completed				0.14
Less than High School	11 (33.3)	8 (34.8)	3 (30.0)	
High School or Beyond	22 (66.7)	15 (65.2)	7 (70.0)	
Race/Ethnicity				.07
Non-Hispanic Black	26 (78.8)	21 (91.3)	5 (50.0)	
Non-Hispanic White	5 (15.2)	0	5 (50.0)	
Hispanic	2 (6.1)	2 (8.7)	0	
Ever had Genital Warts				.99
Yes	5 (15.2)	4 (17.4)	1 (10.0)	
No	28 (84.9)	19 (82.6)	9 (90.0)	
Current Genital Warts				.99
Yes	2 (6.1)	2 (8.7)	0	
No	31 (93.9)	21 (91.3)	10 (100)	
Ever had Anal Warts				.21
Yes	3 (9.1)	1 (4.4)	2 (20.0)	
No	30 (90.9)	22 (95.7)	8 (80.0)	
Current Anal Warts				.24
Yes	3 (9.7)	1 (4.8)	2 (20.0)	
No	28 (90.3)	20 (95.2)	8 (80.0)	
Ever had Gonorrhea				.26
Yes	14 (42.4)	8 (34.8)	6 (60.0)	
No	19 (57.6)	15 (65.2)	4 (40.0)	
Ever had Genital Herpes				.22
Yes	3 (9.4)	1 (4.6)	2 (20.0)	
No	29 (90.60)	21 (95.5)	8 (80.0)	
Ever had Syphilis				.61
Yes	14 (42.4)	11 (47.8)	3 (30.0)	
No	18 (54.6)	11 (47.8)	7 (70.0)	
Ever had Chlamydia				.52
Yes	1 (3.0)	0	1 (10.0)	
No	31 (93.4)	22 (95.7)	9 (90.0)	
Ever had HIV Opportunistic Infections				.43
Yes	16 (50.0)	10 (43.5)	6 (66.7)	
No	16 (50.0)	13 (56.5)	3 (33.3)	
Receptive Anal Sex				.46
Yes	13 (39.4)	8 (34.8)	5 (50.0)	
No	20 (60.6)	15 (65.2)	5 (50.0)	
Oro-Anal Sex				.72
Yes	15 (45.5)	11 (47.8)	4 (40.0)	
No	18 (54.6)	12 (52.7)	6 (60.0)	
Number of Sex Partners Ever	104 (SD=207; R: 5-1000)	68 (SD=143; R: 5-700)	185 (SD=304; R: 10-1000)	
Age at First Sexual Intercourse	13.8 (SD=4.0; R: 5-21)	13.3 (SD=4.4; R: 5-21)	15 (SD=2.49; R: 12-20)	
Currently on HAART				.54
Yes	30 (90.9)	20 (87.0)	10 (100)	
No	3 (9.1)	3 (13.0)	0	
Ever on HAART				.99
Yes	31 (93.9)	21 (91.3)	10 (100)	
No	2 (6.1)	2 (8.7)	0	
Ever Smoke 100 Cigarettes				.06
Yes, current smoker	12 (36.4)	12 (52.2)	0	
Yes, but quit	13 (39.4)	8 (34.7)	5 (50.0)	
No	8 (24.2)	3 (13.0)	5 (50.0)	
Current Alcohol Use				.71
Yes	12 (36.4)	9 (39.1)	3 (30.0)	
No	21 (63.6)	14 (60.9)	7 (70.0)	
Ever Alcohol Use				-
Yes	33 (100)	23 (100)	10 (100)	
No	0	0	0	
Current Cocaine Use				0.29
Yes	5 (15.2)	5 (21.7)	0	
No	28 (84.9)	18 (78.3)	10 (100)	
Ever Cocaine Use				0.33
Yes	27 (81.8)	20 (87.0)	7 (70.0)	
No	6 (18.2)	3 (13.0)	3 (30.0)	
Current Crack Use				.29
Yes	4 (12.1)	4 (17.4)	0	
No	29 (87.9)	19 (82.6)	10 (100)	
Ever Crack Use				.70
Yes	22 (66.7)	16 (69.6)	6 (60.0)	
No	11 (33.3)	7 (30.4)	4 (40.0)	
≥ 1 High-Risk HPV Type (any site)				.23
Yes	25 (86.2)	20 (90.9)	5 (71.4)	
No	4 (13.8)	2 (9.1)	2 (28.6)	
Mean No. of HPV Types by Site				
Penile	2.4 (SD=2.5; R: 0-8)	3.0 (SD=2.6; R: 0-8)	0.57 (SD=0.53; R: 0-1)	
Oral	0.9 (SD=1.2; R: 0-4)	1.0 (SD=1.3; R: 0-4)	0.57 (SD=0.53; R: 0-1)	
Anal	3.3 (SD=2.5; R: 0-10)	3.3 (SD=2.6; R: 0-10)	3.4 (SD=2.4; R: 0-8)	
Individuals with More than Mean No. of Types (any site)				.06
Yes	19 (57.6)	16 (69.6)	3 (30.0)	
No	14 (42.4)	7 (30.4)	7 (70.0)	

Table 1: Demographic and other characteristics of the study population, overall and by Interferon- alpha (IFN) treatment group.

significant differences between groups (likely due to insufficient statistical power), a higher proportion of the IFN-α-untreated group reported being current smokers who have smoked at least 100 cigarettes in their lifetime (52% compared to 0% of treated group), whereas a higher proportion of the IFN-α-treated group reported being non-smokers (50% compared to 13% of untreated group). Only one individual reported not being on HAART at time of enrolment. A higher proportion of the IFN-α-untreated group had more than the average number of HPV types from swabs of at least one sited (about 70% compared to 30% of treated group). The IFN-α-untreated group also had a higher number of different HPV types on average from penile and oral swabs, but not from anal swabs, compared to the treated group. The average numbers of HPV types from anal swabs were very similar between the treatment groups.

Only one individual in this study was HPV-negative (IFN-α-untreated group). Overall, the most common HPV types from the penile swabs were HPV-6, -72, and -84. The most prevalent oral type was HPV-55. From the anal swabs, the most prevalent HPV types were HPV-45 and -70. Numbers were too small to assess whether the prevalence of each HPV type was significantly more common among treated or untreated groups.

To further describe our study population, we also examined HPV infection by relevant demographics other than IFN-α treatment group, such as sexual orientation and education. Among individuals infected with greater than the average number of HPV types at a minimum of one site, 37% reported engaging in sexual intercourse with both men and women, 58% with women only, and 5% with men only. By contrast, among individuals with less than the average number of HPV types, 21% reported engaging in sexual intercourse with both men and women, 50% with women only, and 29% with men only. Highest level of education was not substantially different between individuals infected with more or less than the average number of HPV types; about 36% of each group had at least some college education.

Discussion

This pilot study provides some limited preliminary evidence that IFN-α treatment for HCV may be associated with being infected with fewer HPV types in the penile and oral regions (compared to untreated individuals). However, our findings are based on a very small study population and warrant further examination in a much larger study that is appropriately powered to detect significant differences between treatment groups and sites of HPV infection. Nonetheless, the results from this pilot study present an important contribution to the literature, as this is one of the first studies to begin exploring the potential relationships between pegylated IFN-α and HPV infections of the penile, oral, and anal regions.

There is a paucity of published literature on the potential associations between IFN-α and HPV infection/disease. Some *in vitro* data suggests that IFN-α can eliminate cells that are infected with episomal bovine Papilloma virus [16], but more recent evidence indicates that IFN-α is less efficacious against cells that contain integrated HPV-31 DNA [17]. The few clinical studies that have evaluated the newer formulations of IFN-α in HPV disease have yielded mixed results. Generally, IFN-α has been shown to be efficacious for the treatment of genital warts [19,20], but results have been less consistent for its use in the treatment of cervical dysplasia or high-risk HPV infections [21,24-26]. A clinical trial on the effects of standard (non-pegylated) IFN-α treatment among HIV-negative women did not find it to be efficacious for treating high-risk genital HPV infections [21]. However, this study did not address oral or anal HPV infection. Our study, by contrast, examined the effects of pegylated IFN-α treatment for HCV on oral, anal, and penile HPV infection among HIV/HCV co-infected men.

The questions addressed by this pilot study are of particular significance because HIV-infected Men who have Sex with Men (MSM) are at high risk for persistent anal and penile HPV infections. A prevalence estimate of the latter has not been published, to our knowledge, but HPV prevalence ranges from 52-72% among HIV-negative heterosexual men [27] and is thought to be much higher among HIV-positive MSM [11]. Given that high-risk HPV infection is likely to be causally linked to intraepithelial neoplasiain several squamous tissues (i.e., oral mucosa, anal canal, penis, vulva, and vagina) [6,28], it is not surprising that anal cancer incidence has been reported to be up to 37 times higher among HIV-positive MSM, compared to men in the general population [14], and that penile cancer incidence may be up to four times higher among HIV-infected individuals [15]. Although the results of this pilot study are preliminary and should, therefore, be interpreted with caution, they have provided some rationale for continuing to explore whether pegylated IFN-α may be a useful adjuvant therapy, or whether it could be combined with other treatment modalities for controlling HPV infection (or HPV- associated disease), specifically of the penis or oral mucosa.

This study was subject to limitations typical of small pilot projects. The major limitation of our study was the sample size. There were only 10 individuals in the IFN-α-treated group and 23 in the untreated comparison group. However, this was an exploratory pilot study that was designed simply to generate preliminary data. Future studies have been planned to examine the associations of interest in a much larger study population. Another limitation of our pilot study was related to the cross-sectional nature of data collection. We were unable to follow up with the participants over time, or to obtain pre- and post-treatment measures of HPV infection. Longitudinal data will be collected in future studies and will include multiple measures of HPV presence, type, and viral load over time.

In conclusion, this small pilot study has provided some evidence that the effect of pegylated IFN-α treatment on HPV infection warrants further clarification among HIV/HCV co-infected individuals. Although the numbers of HPV types present in the anal region were similar between treated and untreated groups, there seemed to be a lower number of HPV types present in the penile and oral regions of treated individuals. If these findings are confirmed in a larger study, the biological mechanism behind how the penile and oral regions may be differentially affected by the IFN-α treatment, compared to the anal region, would need to be elucidated.

Acknowledgement

This study was supported by an AIDS Malignancy Consortium/Dan L. Duncan Cancer Center Pilot Award to ME Scheurer.

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Citation: Amirian ES, Chiao EY, Hill KT, Marquez-Do D, Scheurer ME (2013) Preliminary Findings on the Effects of Interferon-α Treatment on Human Papilloma virus Infection in a Small Pilot Study of HIV and Hepatitis C Virus Co-Infected Men. Epidemiol 3: 139. doi:10.4172/2161-1165.1000139