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ORIGINAL RESEARCH

The Impact of an Educational Program on Cervical Cancer Knowledge Among HIV-Positive Women in Bali, Indonesia

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Background: The burden of Human papillomavirus (HPV)-related cancers is expected to rise in Indonesia as there has been an increase in the availability of medication that prolongs the survival of women infected with the human immunodeficiency virus (HIV+). There is an urgent need for cervical cancer (CC) screening to address this concern.

Objective: The objectives of the current study were to determine the burden of HPV infections and cervical pre-cancer lesions and evaluate the effectiveness of an education program to improve HPV and CC knowledge among women attending HIV clinics in Bali, Indonesia.

Methods: A questionnaire focused on HPV and CC was administered to 200 HIV+ women before (pre-education) and after the education program (post-education). Cervical cells were used to perform the Papanicolaou (Pap) and test for 13 high-risk (HR) HPV genotypes. Women diagnosed with Pap diagnoses of greater than atypical squamous cells of undetermined significance (≥ASCUS+) were identified as abnormal Pap.

Results: Fifty-four percent of women were diagnosed with ASCUS+ and 81% of those women were positive for any one of the 13 HR-HPV genotypes while 71% were positive for any HPV genotype included in the 9-valent (9V) HPV vaccine. The percentages of women who answered questions correctly at the pre-education interview was 3–25% while 97–100% gave the correct answers to the same questions at the post-education interview ($P<0.0001$).

Conclusion: Our study for the first-time documented that a significant proportion of women who attend HIV clinics in Bali are diagnosed with ASCUS+ and HR-HPVs which put them at high risk for developing CC. It would have been possible to prevent the development of ASCUS+ in at least 70% of those women if 9V HPV vaccine was given to these women. Since all 200 women educated by our program consented for screening, we clearly demonstrated that HIV+ women attending HIV clinics can be successfully educated to participate in CC screening.

Plain Language Summary: When women infected with the human immunodeficiency virus (HIV) live longer because of the availability of HIV medications, more women are likely to develop cervical cancer (CC) caused by another virus called the human papillomavirus (HPV), a common infection in HIV infected women. Therefore, there is an urgent need for CC screening to address this concern. Participation in CC screening is low in developing countries like Indonesia. Since several studies have shown the need for education programs to improve cancer screening rates of women at high risk for developing CC in such countries, we conducted a study to test the burden of HPV infections and cervical pre-cancer lesions and evaluate the effectiveness of an education program to improve HPV and CC knowledge among women attending HIV clinics in Bali, Indonesia. We observed that more than 50% of women have cervical pre-cancer lesions and 81% of those women are also infected with cancer causing HPVs. We also observed that the percentages of women who answered questions correctly at the pre-education interview was 3–25% while 97–100% gave the correct answers to the same questions at the post-education interview. Since all 200 women educated by our program consented for screening, we clearly demonstrated that women attending HIV clinics can be successfully educated to participate in CC screening, an important step to lower the risk of developing CC in HIV infected women.

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Introduction

An estimated 3.5 million people live with HIV in the South-East Asia Region.[1] Five countries, namely, India, Indonesia, Myanmar, Nepal, and Thailand account for the 99% of HIV infections in this region.[1] The World Health Organization (WHO) estimates that 73,000 people get infected with the virus per year in Indonesia, only behind China and India where the key populations at higher risk for acquiring HIV in these countries include sex workers/their clients, men who have sex with men, transgender and bi-sexual people or who inject drugs.[2] A downward or stable trend of new HIV infections from 2000–2015 occurred in four of these countries with the exception of Indonesia where the HIV epidemic is still on the rise.[2,3] Further, HIV cascade data among key populations in Indonesia has shown poor rates of retention in treatment and viral suppression.[4] However, therapy with combination antiretroviral therapy (cART) that reduces the risk of acquired immune deficiency syndrome (AIDS) has become more available to the HIV infected (HIV+) population in Indonesia in recent years by establishing Voluntary Counselling and Testing (VCT) clinics that provide such medications to HIV+ individuals. Because of this, we expect a prolonged survival of HIV+[5] in Indonesia in the near future. Prolonged exposure to HR-HPVs that causes cervical pre-cancer and CC that accompany a longer survival time will lead to a higher incidence and prevalence of those lesions in this population.

Women affected by HIV worldwide[6–8] are significantly more likely to acquire infection with high risk (HR)-HPVs, the causative agent for developing cervical intraepithelial neoplasia (CIN) and cervical cancer (CC), an AIDS-defining cancer.[9–11] Therefore, the burden of HPV-related cancers is expected to rise in Indonesia compared to the other four countries. Since women represent almost 50% of all adults living with HIV worldwide,[12] it is imperative that HIV+ women do not succumb to CC, largely a preventable disease. CC is the most known cancer caused by HR-HPVs globally, affecting 530,000 women each year and leading to 275,000 deaths annually. If this current trend continues, by the year 2050, it is estimated that there will be more than one million new cases annually.[13] CC is the third most common cancer worldwide, and ~85% of cases occur in the developing world.[14] CC mortality is 18-fold higher in resource poor countries than in resource rich developed countries.[15] CC is the most common cancer among Indonesian women where 20,928 new CC cases are diagnosed and 9498 deaths occur annually.[16,17] Therefore, it is important to implement novel, cost-effective and evidence-based screening approaches to identify those at high risk for CC at the earlier stages with greater accuracy to provide essential medical care before CC becomes a major health burden.[18] This long-term goal can only be achieved if women participate in regular CC screening programs and receive treatments to remove higher grades of CIN in a timely manner and accept preventive measures such as prophylactic HPV vaccines when eligible to receive those vaccines.

Similar to other developing countries, the participation in CC screening is low in Indonesia. Several studies have shown the need for education programs to improve cancer screening rates in such countries.[19] The main obstacles to CC screening in developing countries include lack of trust, inadequate knowledge about CC, where to seek screening, cost of tests, fear of hospitals, pain or embarrassment from the procedure, limited access to such services, lack of healthcare provider recommendations for screening, delays in receiving test results and no follow-up on care needed when identified as high-risk for developing CC.[20–23] In addition, cultural beliefs and societal factors significantly influence CC screening and education in Indonesia often leading to stigma that discourages women seeking necessary medical care. In many Indonesian communities, topics related to reproductive health, including CC are considered a taboo. This cultural reluctance to engage in open discussions can result in misinformation and a lack of awareness regarding the importance of screening.[24] Further, the lack of comprehensive reproductive health education in schools and communities exacerbates this issue as many adolescents and young women grow up without adequate knowledge about CC and its prevention.[25,26]

Several studies and WHO reports collectively have shown the benefits of educational programs to improve CC screening behavior in developing countries.[27–31] and even in rural communities along the US-Mexico border.[32] Studies of similar nature have also been used successfully in promoting prostate and CC screening behavior in similar settings.[33–36]

Based on this background, the objectives of the current study were to determine the burden of HPV infections and cervical pre-cancer lesions and evaluate the effectiveness of an education program to improve HPV and CC knowledge among HIV+ women attending VCT clinics in Bali, Indonesia.

Materials and Methods

Study Population

The study population consisted of 200 HIV+ women who attended 6 VCT clinics in Bali, Indonesia. The study was approved by the Institutional Review Board of the University of Alabama at Birmingham (UAB) and the Ethics committee of the Udayana University, Bali. All study protocols were in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All women gave their informed consent prior to their inclusion in the study.

Methods

Education Program

A study staff member with a background in health education who was trained by study investigators administered a pre-tested and validated questionnaire focused on HPV and CC to all women prior to administering an education program (pre-education) and after (post-education). We administered 16 questions that are related to HPV and CC knowledge. All study participants were given an opportunity to ask questions if any of the questions were unclear to them.

Cervical Cell Collection

Cells were collected using the contoured end of the plastic spatula and by rotating 360 degrees around the entire exocervix while maintaining tight contact with exocervical surface. The spatula was rinsed quickly into the vial solution by swirling the spatula 10 times. An endocervical brush device was used to collect adequate sample from the endocervix by inserting the brush into the cervix until only the bottom-most fibers remain exposed and by slowly rotating ¼ - ½ turn in one direction. This brush was rinsed in the vial solution by rotating the device in the solution 10 times while pushing against the PreservCyt vial wall and by swirling the brush vigorously to further release of cells. Vial caps were tightened to avoid leakage of the collected sample. All cervical samples were collected by a nurse midwife trained by Gynecologists at VCT clinics.

Cytology

After keeping a 5 mL aliquot from each patient sample for the HPV assay, samples were sent to the ISO certified clinical diagnostics laboratory at BaliMed hospital where the Papanicolaou (Pap) test was performed using ThinPrep 2000, Cytyc Corporation and evaluated for the status of Pap diagnoses.

HPV Test

HPV genotype status was assessed using the HPV XpressMatrix™ Genotyping Kit based on the use of target amplification and hybridization methods for the detection of 13 HR-HPV genotypes and 6 LR-HPV genotypes in KalGen DNA diagnostics laboratory in Jakarta Indonesia. Highly satisfactory analytical sensitivity and specificity of this assay has been documented using a panel of WHO cloned HPV Plasmid DNA by the KalGen DNA diagnostics laboratory.

Statistical Analysis

Based on HPV genotype results, women were categorized as HR-positive when tested positive for any one of the 13 HR-HPV genotypes (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and as negative when tested negative for all 13 HR-HPV genotypes. Pap diagnoses of atypical squamous cells of undetermined significance (ASCUS), low or high-grade squamous intraepithelial lesion (LSIL, HSIL), collectively as ASCUS+ was coded as abnormal Pap and negative for intraepithelial lesions or malignancy (NILM) was coded as normal Pap diagnosis. Women were categorized into groups based on Pap and HPV test results as ≥ASCUS+ or NILM and negative for all HR-HPVs, positive for any one of the 13 HR-HPVs; positive for any quadrivalent (QV) HR-HPV (16 or 18) and ± for any other HR-HPV; positive for any

9-valent (9V) HR-HPV (16, 18, 31, 33, 45, 52 or 58) and ± for any other HR-HPV; negative for all Qv HR-HPVs and positive for any other HR-HPV and negative for all 9V HR-HPVs and positive for any other HR-HPV.

The independent association between HR-HPV and the likelihood of having ASCUS+ was evaluated using unconditional multivariable logistic regression analyses models. The independent variables in the model included either continuous age or a dichotomous categorical variable for age greater than or equal to median age, and categorical variables for education less than high school vs high school education or higher, parity defined as had at least one child, and HPV status (negative for all HR-HPVs vs positive for any HR-HPV genotype and each of the HR-HPV positive groups defined above). SAS® version 9.4 (SAS Institute, Cary, NC, USA) was used for all statistical procedures.

For each question in the pre- and post-education questionnaires, a binary variable indicating correct as 1 versus incorrect as 0 was assigned based on the correct responses for each question. Text response questions were deemed correct if greater than or equal to 3 correct text responses were provided by the participant. The sum of the number of correctly answered questions was calculated and then divided by the total number of questions assessed to derive the percentage of correctly answered questions in each pre- and post-education questionnaire. A paired *t*-test statistic was used to evaluate if there is statistical evidence that the mean difference between participants' paired observations for sum of the correct scores in pre-test and sum of correct scores in post-test was significantly different than zero. A McNemar's test determined if there is a statistically significant difference for each of the 16 questions correct response binary variable for pre-test compared to post-test correct response binary variable. The null hypothesis tested was that the education program had no effect on improving HPV and CC knowledge. The frequencies of correct response for pre and post-test were equal for each of the 16 questions. The test statistic was a chi square statistic with 1 degree of freedom.

Results

The age range of the women included in the study was 18–68 years with a median age of 38. Fifty-four percent of women diagnosed with ASCUS+ had age greater than or equal to the median age whereas 48% diagnosed with NILM had age greater than or equal to the median age. Twenty-nine percent of those with ASCUS+ had less than a high school education whereas 25% of those with NILM had less than a high school education. Overall, 27% of women had less than a high school education. Eighty percent of those diagnosed with ASCUS+ had at least one child whereas 77% of those diagnosed with NILM had at least one child. Overall, 78% of women had at least one child.

Overall, in this population of 200 women, 47% of women tested positive for any one of the 13 HR-HPV genotypes while 21% and 41% were positive for any HR-HPV included in the QV and 9V HPV vaccines, respectively. The distribution of women by HPV result and Pap diagnoses is shown in Figure 1. We observed that 81% of women diagnosed with ASCUS+ were positive for any one of the 13 HR-HPV genotypes and that 36% and 71% were positive for any HPV genotype included in the QV and 9V HPV vaccines, respectively. Further, 46% and 10% diagnosed with ASCUS+ were negative for QV HR-HPVs but positive for any other HR-HPV and negative for 9V HR-HPVs but positive for any other HR-HPV, respectively. Women diagnosed with any HR-HPV were 11.17 times more likely to be diagnosed with ASCUS+ compared to women negative for all HR-HPVs detected by the HPV test (Table 1). Slightly higher Odds ratio (OR) of 12.55 was noted for women who tested positive for QV HPV vaccine genotypes while a similar OR of 11.42 was observed for women who tested positive for any 9V HPV genotype in alternative models that controlled for the same independent variables shown in Table 1. None of the other variables were significantly associated with the likelihood of being diagnosed with ASCUS+ in any model.

Sixteen questions focused on HPV and CC knowledge that were administered in the education program are shown in Table 2. Percentages of women who answered the 16 questions correctly, pre and post education are shown in Figure 2. The percentages of women who answered questions correctly at the pre-education interview was 3–25% while 97–100% gave the correct answers to the same questions at the post-education interview. The McNemar's test comparing frequencies of correct answers for pre- and post-education interview were statistically significant for each question asked ($P<0.0001$).

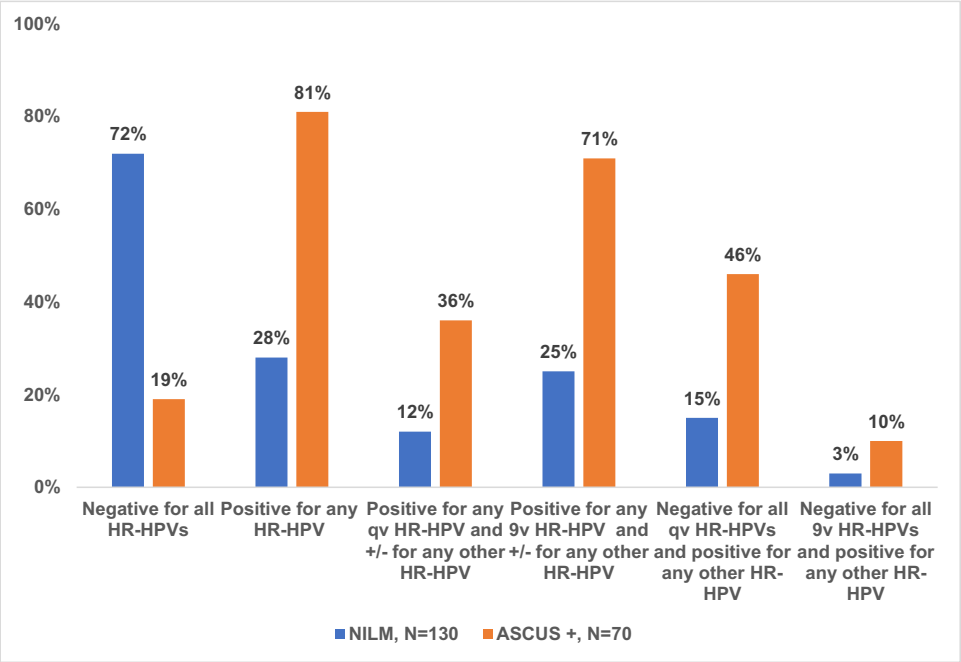

Figure 1 The distribution of 200 women by HPV results and Pap diagnoses.

Discussion and Conclusions

Pap test has been the gold standard for CC screening for more than 50 years because of its effect on lowering CC mortality when regular screening is based on this test.[37–39] However, since recent scientific evidence illustrates that HPV testing is more sensitive than the Pap test, WHO recommends implementation of primary HPV screening in countries where Pap-based screening programs do not exist or are ineffective.[40] Currently, HPV DNA testing combined with Pap test, known as "co-testing", is approved for screening as combining these tests results in improved identification of women with pre-cancer lesions or CC.[41]

Table 1 The Associations Between Demographic and Lifestyle Factors and HPV Genotype Categories and Risk of Being Diagnosed with ASCUS+

	NILM vs ASCUS+	
	OR (95% CI)	**P-value**
Age ≥ median age	1.34 (0.67–2.70)	0.4121
Educational level		
High school education or higher	1.00	
Less than high school education	1.20 (0.55–2.60)	0.6455
Parity		
0 live birth	1.00	
≥ 1 live birth(s)	1.03 (0.44–2.38)	0.9478
HPV status		
Negative for all HR-HPVs	1.00	
Positive for any HR-HPV	11.17 (5.44–22.95)	<0.0001

Table 2 Sixteen Questions Focused on HPV and CC That Were Administered in the Education Program

#	Questions
1	HPV is a virus that is sexually transmitted
2	Unprotected sexual relationships can increase the probability of HPV infection
3	The following can lower your risk of an infection with HPV: a lower number of sexual partners, being a non-smoker, receiving a HPV vaccine, eating a healthy diet or using condoms (knew 3 or more correct answers)
4	If high-risk HPV persists in the cervix, it can cause cervical cancer in women
5	Nearly all cervical cancers are caused by an infection with HR-HPVs
6	An infection with HR-HPVs can cause cancer of the cervix, vagina and vulva in women, penile cancer in men and oropharyngeal and anal cancer in both sexes
7	Symptoms are always present with an HPV infection
8	There is a cure for HPV infections
9	Symptoms of cervical cancer that you may experience include bleeding after sexual intercourse, pelvic pain, abnormally long or heavy periods or vaginal bleeding (knew 3 or more correct answers)
10	Screening is the most important tool to detect HPV infection before it develops into cervical cancer
11	Yearly screening for cervical cancer is recommended by the Pap and/or HPV test for those who are 25 years or older and tested positive for an infection with the *human immunodeficiency virus* (HIV)
12	A Pap and HPV test is conducted by a healthcare worker by inserting a speculum into the vagina and then using a swab to take samples of the cervical cells
13	A Pap smear screening test and/or testing for HPV can reduce your risk of developing cervical cancer
14	Cervical cancer is the 2nd or 3rd leading causes of cancer deaths among women in developing countries
15	Women infected with HIV are at a higher risk for contracting HPV and for developing HPV-related cancers
16	Based on the information you received today, do you want to get screened for cervical cancer?

In most developing countries, the prevalence of abnormal Pap lesions or HPV infections are largely unknown due to lack of CC screening programs. Our study for the first-time documents that a substantial proportion of HIV+ who attend VCT clinics in Bali are diagnosed with abnormal ASCUS+ which puts them at risk for developing CC. Our results also

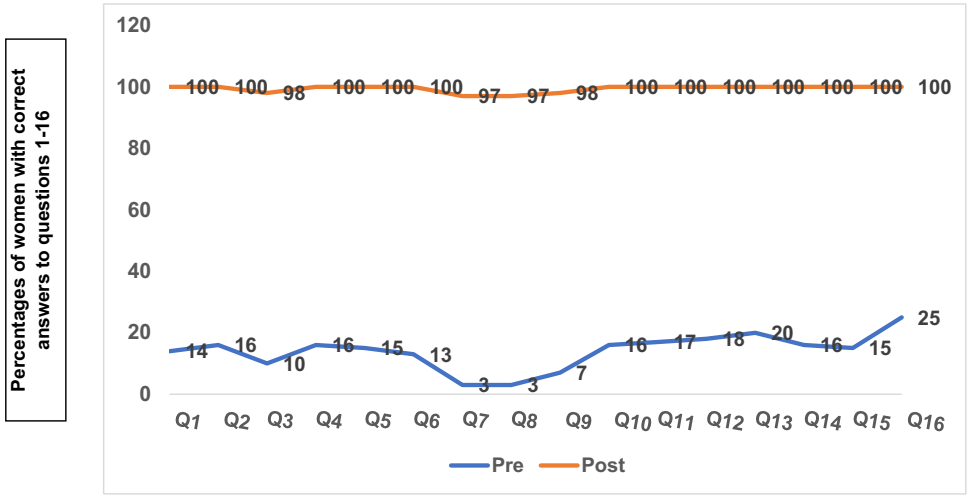

Figure 2 Percentages of women who answered 16 questions that are focused on HPV and CC knowledge correctly at pre and post education interviews.

showed that 81% of women diagnosed with ASCUS+ were positive for any one of the 13 HR-HPV genotypes, again demonstrating their higher risk of developing CC as HR-HPV is the main causative agent for developing CC. Our observation that 36% and 71% of women diagnosed with ASCUS+ tested positive for HPV types included in QV and 9V HPV vaccines, respectively, indicated that the 9V vaccine is more beneficial compared to the QV in preventing the development of those ASCUS+ lesions. Currently, HPV vaccine availability, especially 9V is very low in Indonesia and the vaccine acceptability is also low in the country. Our results demonstrated the importance of HPV vaccines for CC prevention in this population. We also noted that currently available vaccines will not prevent the development of CC entirely in this population since there were ASCUS+ lesions related to infections with HR-HPV genotypes that are not included in such vaccines. Therefore, other preventive measures are necessary to control the residual risk of developing CC even in vaccinated women.[42] Such preventive approaches, especially should target screening of women with risk factors for CC, such as smokers, contraceptive users, women with higher parity, higher number of sexual partners and those who consume unhealthy diets that lack cancer protective micronutrients. Our previous studies conducted in USA[43–46] and in India[47] have demonstrated the importance of specific micronutrients or overall dietary patterns for the prevention of HR-HPV related pre-cancer.

In our education program results, we especially noted that after the education program, 100% of women understood that sexually transmitted HR-HPVs that persist is a risk factor for developing CC and participation in annual screening by Pap and HPV testing is important to prevent the development of CC especially when infected with HIV+ as they are at higher risk for CC. Also, after the education program, 100% of women understood how the Pap and HPV testing is done by the health care provider. As a result, all 200 women educated by our program consented for those tests. These results clearly demonstrated that HIV+ women who attend VCT clinics can be successfully educated to participate in CC screening. This is a significant observation since currently those women are not screened for CC risk by the VCT clinics. We hope that VCT clinicians will utilize our findings and implement CC screening and other preventive programs in VCT clinics to manage these women who are at substantial risk for developing CC. Since there are well functioning VCT clinics all over the Bali Island, establishment of successful CC screening programs in those clinic settings will facilitate the enrolment of HIV+ women for larger studies that are needed to test the efficacy of screening protocols with higher accuracy to identify HIV+ at higher risk for CC using evidence-based and novel but cost-effective approaches. We envision that Bali can serve as a model to expand our approaches to other Islands of Indonesia as well as other developing countries with similar HIV burden to control not only CC but also other HR-HPV related cancers such as anal cancer, especially in HIV+ men who have sex with men (MSM) who are also seen at HIV clinics. Studies in other countries have suggested that integrating HIV counseling and CC screening significantly improved the awareness and screening uptake where such integration was also found to be manageable in a clinical setting.[48]

Even though our study findings provide much needed and timely insights that can shape public health policies and practices aimed at improving CC prevention among HIV+ women in Bali and similar developing country settings, we emphasize that our study fundings are only applicable to our study population and the possible impact of unmeasured variables on reported findings cannot be excluded in this study. In addition, because of the post education questionnaire was administered soon after education, we cannot assure that the education program will improve regular annual screening required to prevent CC in an ideal set up. Therefore, the reproducibility of findings in larger studies that allow to control for other relevant factors and gather information such as HPV vaccine acceptability and with prospective follow-up of women in Indonesia as well as in similar developing countries is needed to increase the scientific credibility of our current study findings.

In conclusion, we documented that a substantial proportion of HIV+ who attend VCT clinics in Bali are at high risk for developing CC and providing 9V HPV vaccine could have prevented the development of ASCUS+ in at least 70% of those women. Since all 200 women educated by our program consented for screening tests, we clearly demonstrated that HIV+ women who attend VCT clinics can be successfully educated to participate in CC screening and this approach is expected to lead to an overall reduced risk of CC in this high-risk population.

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Disclosure

The authors report no conflicts of interest in this work.

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