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Persistence and clearance patterns of cervical high risk human papillomavirus (Hr-HPV) infections in women with negative cytology results in Harare, Zimbabwe

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Abstract
Background: Persistent Hr-HPV infection is a prerequisite for cervical carcinogenesis. Knowledge of the persistence or clearance patterns of specific Hr-HPV genotypes can help clinicians to formulate interventions to prevent the development of cervical cancer.
Objectives: To determine the persistence and clearance patterns of Hr-HPV infections in Zimbabwean women and to compare the persistence or clearance rates of different Hr-HPV genotypes.
Design: Cross sectional descriptive study.
Setting: Cimas Medical Laboratories and KAVI molecular laboratory.
Subjects: Women with Hr-HPV infections and NILM cytology results on baseline assessment.
Materials and Methods: The women were followed up for 24 months and retested for the presence of Hr-HPV DNA. Hr-HPV testing was done using the HPV Genotypes 14 Real-TM Quant test kit. The Hr-HPV persistence rates in women <30 years and those ≥30 years old was compared using an independent t-test. A p-value <0.05 was regarded as statistically significant.
Results: A total of 52 women met the study inclusion criteria**.** The mean (SD) age of the study participants was 33.5 (5.5) years. Persistence and clearance rates were 34.6% [18/52] and 65.4% [34/52] respectively. The Hr-HPV clearance rates of women <30 years and those ≥ 30 years old were comparable (53% [18/34] vs. 47% [16/34], respectively; p=0.642). HPV 16 and 52 were the most persistent genotypes: 53.8% and 37.5% respectively. HPV 35 and 51 had the highest clearance rates of 100%.
Conclusion: HPV 16 and HPV 52 were the most persistent Hr-HPV genotypes; and HPV 35 and HPV 51 had the highest clearance rates in Zimbabwean women.

Keywords: human papillomavirus, cervical cancer, persistent, clearance, cytology

Introduction
Cervical cancer is ranked as the 3rd most common malignancy in women and is the 4th leading cause of mortality in women worldwide [1]. However, it is the most common malignancy in Zimbabwe regardless of gender [2]. Cervical cancer cause 35% of all cancer related deaths in Zimbabwe [2].

The establishment of a cause – effect association between Hr-HPV and cervical cancer prompted the inclusion of Hr-HPV DNA testing in the cervical cancer screening algorithms [3]. HPV is the most common sexually transmitted infection in reproductive women with >75% of them having been infected by HPV at some point in their lifetime [3]. They infect the basal keratinocytes of the cervical stratified squamous epithelium during sexual contact [4]. Numerous (>100) HPV genotypes are known [5]. Only the high risk genotypes such as 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82 are associated with genital precancerous and cancerous lesions.[5] Low risk genotypes such as 11, 44, 54, 61, 70, 72, and 81 have a low neoplastic potential and only causes benign genital warts [5].

Most of the infections (>90%) are transient and are cleared by the host cell mediated immunity within 24 months [6]. Persistence or clearance patterns of HPV vary based on the age of the patient, HPV genotype, immune status and sexual behaviour of the patient [6]. HPV has a higher clearance rate in women less than 30 years than in women above 30 years because of competent cell medicated immune systems in the younger patients [7]. HPV persist in only a minority of women with the ultimate result being; the abnormal proliferation of the cervical epithelium [7]. Persistent Hr-HPV infection is therefore, a pre-requisite for cervical neoplasia because Hr-HPV

is detected in >99% of cervical cancer cases.[5] In a study by Miranda *et al*. in Brazil, an HPV persistence rate of 59.6% was reported in women [2].
There is paucity of reliable information regarding clearance or persistence patterns of genital Hr-HPV in Zimbabwe. This information is important in order to predict the possible clinical outcomes. Therefore, this study was aimed at investigating the Hr-HPV persistence or clearance patterns in Zimbabwe and to identify women with persistent Hr-HPV infections for closer follow up.

2. Material and Methods

2.1. Study design: Cross-sectional descriptive study from January 2019 to May 2021.

2.2. Sampling method: Consecutive sampling method.
2.3. Study population: Women with Hr-HPV infections and NILM cytology results on baseline assessment.

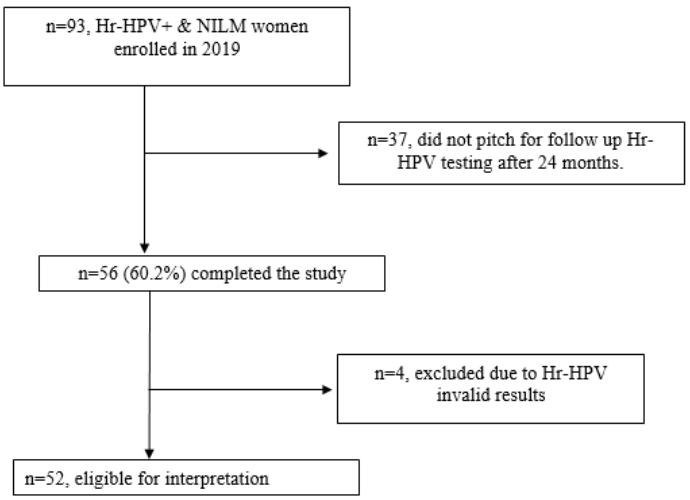
2.3.1. Inclusion criteria: No previous history of cervical cancer.
2.3.2. Exclusion criteria: Women with invalid Hr-HPV results on any one of the two visits.

2.4. Study sites: Cimas Healthcare Clinics, Cimas Medical Laboratories and KAVI molecular laboratory.

2.5. Study objectives

1. To determine cervical Hr-HPV persistence and clearance rates in Zimbabwean women.
2. To compare the Hr-HPV clearance rates between women <30 years and ≥ 30 years using the independent t-test.
3. To compare the persistence and clearance rates of different HR-HPV genotypes.

2.6. Sample size and recruitment of study participants.



Abbreviations: NILM -Negative for intraepithelial lesion on Pap smear, Hr-HPV-High risk Human Papillomavirus

2.7 Hr-HPV DNA testing

Cervical samples were collected using Cervex brushes and preserved in ThinPrep PreservCyt (Hologic, Marlborough, MA) solution. Hr-HPV DNA testing was done using the HPV Genotypes 14 Real-TM Quant test kit (Sacace Biotechnologies - 44 – 22100, Como, Italy) according to manufacturer's specifications. This is a qualitative test detects 14 high risk HPV types : HPV 16,18, 31,33,35,39,45, 51,52,56,58,59,66 and 68).

2.8. Ethical considerations

Ethical approval was obtained from the Joint Research Ethical Committee of University of Zimbabwe and Parirenyatwa Hospital (JREC), certificate number: JREC 119/2020. Informed consent was sought form the participating women. Permission was also granted by Cimas MEDLABS. During the study, strict patient confidentiality was observed. Cervical sample collection is a safe procedure; however, a few minor and self limiting complications such as mild bleeding were encountered in patients with cervicitis.

2.9 Data management

The data was analyzed using SPSS version 25. The Hr-HPV persistence rates in women <30 year and those ≥30 years old was compared using an independent t-test. A p-value <0.05 was regarded as statistically significant.

3. Results and Discussion

A total of 93 women (Hr-HPV positive and NILM at baseline assessment) were enrolled into the study in 2019. However, only 56 (60.2%) completed the study after 24 months. Four were excluded from the analysis because they had invalid HR-HPV results on follow up. Therefore findings from 52 women were analyzed in this study.

3.1. Age characteristics of study participants

The mean (SD) age of the final 52 study participants was 33.5 (5.5) years. The age characteristics were stratified into those <30 and those ≥30 years and summarized in Table 1 below:

Table 1: Age characteristics of study participants

Population	≥ 30 years	< 30 years
Number	31	21
Mean age (years)	39.6	27.3
Age SD (years)	8.1	2.9
Age range (years)	30-81	18-29

3.2. HPV persistence or clearance rates

Persistence and clearance rates were 34.6% [18/52] and 65.4% [34/52] respectively. The Hr-HPV clearance rates of women <30 years and those ≥ 30 years old were comparable (53% [18/34] vs. 47% [16/34], respectively; *p*=0.642).

3.3. Loss to follow up

In this study, n=37/93 women (39.8%) were lost during follow up. The major reason to follow up was change of contact details (n= 21/37, 57%) which made the patients to be unreachable. The other reasons for loss to follow up are summarized in the Figure 1 below:

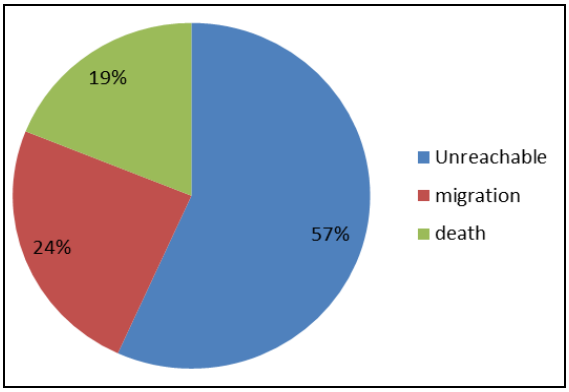


Fig 1: Reasons for loss of follow up

3.4. Persistence and Clearance rates for each Hr- HPV genotype

Five of the women enrolled (n=5/52, 9.6%) had multiple HPV genotypes on baseline assessment: 4 had two Hr-HPV genotypes and 1 had three Hr-HPV genotypes. Therefore, a total of 58 Hr-HPV infections were evaluated for persistence or clearance. HPV 16 was the most persistence stain (53.8%) followed by HPV 52 that had a persistent rate 37.5%. HPV 35 and 51 had the highest clearance patterns of 100%. The other patterns are summarized in Table 2 below:

Table 2: Persistent and Clearance rates for each Hr-HPV genotype

Hr-HPV genotype	Persistent		Cleared	
	n	*f*	n	*F*
16	7	53.8%	6	46.2%
18	2	25.0%	6	75.0%
31	1	25.0%	3	75.0%
33	2	22.2%	7	77.8%
35	0	0.00%	2	100%
45	1	33.3%	2	66.7%
51	0	0.00%	2	100%
52	3	37.5%	5	62.5%
56	1	25.0%	3	75.0%
68	1	20.0%	4	80.0%
Total	19		39	

3.5. Discussion

This study evaluated the persistence or clearance patterns of Hr-HPV in Zimbabwean women with negative cytology baseline results. The Hr-HPV positive women were followed up for 24 months and retested for Hr-HPV again. The Hr-HPV persistence and clearance rates were 34.6% and 65.4% respectively. It is documented that more than 90% of cervical Hr-HPV infections clear within 24 months [8].

The Hr-HPV persistence rate in this study was lower compared to studies by Miranda *et al.* in Brazil (59.6%), Banura *et al.* in Uganda (68.8%) and Guo *et al.* in China (45.7%) [3, 9, 10] The high persistence in these studies could be attributed to the recruitment of some women with cervical squamous intraepithelial lesions (SILs) unlike this study that exclusively enrolled women with negative for intraepithelial lesion (NILM) cytology results on baseline assessment. Women with cervical intraepithelial lesions are more likely to harbor persistent Hr-HPV strains than women with negative cytology results [11]. In addition, the follow up interval in the studies: Banura *et al.* (18.5 months) and Guo *et al.* (14.5 months) *et al.* were shorter than the 24 months used in this study [9, 10]. Evaluation for Hr-HPV persistence before 24 months can result in higher persistent rates because most of the infections will still be active.

Sammarco *et al.* and Syrjanen *et al.* reported that younger women <30 years were more likely to clear their HPV infections compared to older women (≥ 30 years) [12, 13]. This is because younger women have more competent cell medicated immunities capable of eliminating the infections compared to older women [14]. These facts were supported by a study by Castle *et al.* who demonstrated that Hr-HPV persistence increased with age [15]. However, such an association was not found in this study as there was no significant statistical difference in the persistence patterns in women <30 years old and those ≥30 years old. Miranda *et al.* was also not able to demonstrate such an association in their study [3]. This may possibly be explained by the small sample sizes in these two later studies. We postulate that more conclusive findings could have been reached had the studies followed up more women.

It is documented that women infected with multiple Hr-HPV genotypes are more likely to have higher Hr-HPV persistence rates compared to women with single Hr-HPV genotypes. In this study, 9.6% women had multiple Hr-HPV genotypes. This was considerably lower than the 22.2% in the Miranda *et al.* study [3]. This may have contributed in a higher persistence rate (59.6%) in that study compared to the 34.6% in this study.

Regarding persistence or clearance of specific Hr-HPV genotype, HPV16 was the most persistent (53.8%). This differed with Miranda *et al.* who reported that HPV 33,59,66,69 and 83 to be the most persistent genotypes (100%).[3] In addition, HPV 52 was the second most persistent in Zimbabwe. The HPV 52 genotype was not even detected in Brazilian women.[3] This shows great diversity in Hr-HPV genotypes in different populations.

The main limitation for this study was the small sample size. A significant number of women (n=93) were enrolled at the beginning of the study; however, there was a higher loss of follow up (39.8%). This number is comparable to the loss of follow up in the study by Miranda *et al.* (33.1%) [3]. These studies had comparable loss of follow up after the same interval (24 months). However, the loss to follow up after 12 months in a study by Akaaboune *et al.* was 28.1% [16]. This finding raises the suspicion that the longer the follow up periods, the higher the rate of loss to follow up. In this study, the major reason for loss of follow up was change of patient contact details (n=21/37, 56.8%) which made them to be unreachable. Change of place of residence to far areas (n=9/37, 24.3%) and deaths of patient (n=7/37, 18.9%) were the other reasons. Only loss to migration could have been avoided if the study had enough resources to follow up people to distant towns and to neighboring countries.

4. Conclusion: HPV 16 and HPV 52 were the most persistent Hr-HPV genotypes; and HPV 35 and HPV 51 had the highest clearance rates in Zimbabwean women.

5. Recommendation: Patients positive for HPV 16 and 52 on baseline assessment should be followed up closely up so that interventions can be done before the development of cervical cancer.

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7. References

1. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Available from: http://doi.org/10.3322/caac.21492. Accessed on 15.12.18.
2. National cancer prevention and control strategy for Zimbabwe : 2013-17. Available from: https://www.iccpportal.org/sites/default/files/plans/CANCER%20STRATEGY%20FINAL%202013%202017.pdf.Accessed on 25.02.19.
3. Miranda PM, Silva NTT, Pitol BCV, Silva ID, Lima-Filho JL, Carvalho RF *et al*. Persistence or Clearance of Human Papillomavirus Infections in Women in Ouro Preto, Brazil. BioMed Research International 2013, 1-6.
4. Willbur DC, Henry MR. College of American Pathologists Practical Guide to Gynecologic Cytopathology-Morphology, Management and Molecular methods. 1st

edition. CAP Press. Illinois 2008, 1-274.
5. Gómez DT SJ. Human Papilloma infection and cervical cancer: Pathogenesis and epidermiology. VA M. Guadalajara; 2007: Formatex. Available from Citeseerx.ist.psu.edu/viewdoc/versons;jsessionid=F193788F. Accessed on 18.04.19.
6. Confortini M, Carozzi F, Zappa M, Ventura L, Iossa A, Cariaggiet P *et al*. Human papillomavirus infection and risk factors in a cohort of Tuscan women aged 18–24: results at recruitment. BMC Infectious Diseases. 2010;10:157.
7. Wright TC, Massad LS, Dunton CJ. Updated consensus guidelines for the management of women with abnormal cervical cancer screening tests. Am J Obstet Gynecol. 2007;197(4):346-355.
8. Gravitt PE. The known unknowns of HPV natural history. Journal of Clinical Investigation 2011;121(12):4593-4599.
9. Banura C, Sandin S, van Doorn L. Type-specific incidence, clearance and predictors of cervical human papillomavirus infections (HPV) among young women: A prospective study in Uganda. Infectious Agents and Cancer. 2010; 5(1).
10. Guo Y, You K, Qiao J, Zhao Y, Liu C, Geng L. Natural history of infections with high-risk HPV in Chinese women with abnormal cervical cytology findings at baseline. International Journal of Gynecology and Obstetrics 2010;110 (2):137-140.
11. Anderson J, Lu E, Sanghvi H, Kibwana S, Lu A SH. Cervical Cancer Screening and Prevention for HIV-Infected Women in the Developing World. Cancer prevention- from mechanisms to transitional benefits. 2012, 231-4. Available from www.intechopen.com. Accessed on 12.03.19.
12. Sammarco ML, Del Riccio I, Tamburro M, Grasso GM, Ripabelli G. Type-specific persistence and associated risk factors of human papillomavirus infections in women living in central Italy. European Journal of Obstetrics and Gynecology and Reproductive Biology 2013;168(2):222-226.
13. Syrj¨anen S, Shabalova I, Petrovichev N. Factors predicting persistence of high-risk human papillomavirus (HPV) infections in women prospectively followed-up in three new independent states (NIS) of the former Soviet Union. European Journal of Gynaecological Oncology. 2005;26(5):491-498.
14. Lonky N, Mahdavi A, Wolde-Tsadik G, Bajamundi K, Felix J. Evaluation of the clinical performance of high-risk human papillomavirus testing for primary screening. J Low Gen Tract Dis. 2010;14(3):1089-2591. doi: 10.1097/LGT.0b013e3181cc3f3e.
15. Castle PE, Rodriguez AC, Burk RD. Long-term persistence of prevalently detected human Papillomavirus infections in the absence of detectable cervical precancer and cancer. Journal of Infectious Diseases 2011; 203(6):814-822.
16. Akaaboune M, Kenfack B, Viviano M, Temogne L, Catarino R, Tincho E *et al.* .Clearance and persistence of the human papillomavirus infection among Cameroonian women. Womens Health 2018, 14. doi: 10.1177/1745506518805642.