

African Collaborative Center for Microbiome and Genomics Research (ACCME)

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African Collaborative Center for Genomics and Microbiome Research

- Led by Institute of Human Virology, Nigeria
- Collaborating African Institutions:
 - Center for Infectious Diseases
 Research, Zambia
 - National Hospital, Abuja, Nigeria
 - University of Abuja Teaching Hospital, Gwagwalada, Nigeria
 - University of Ibadan, Nigeria
 - African University of Science and Technology, Abuja, Nigeria

- Collaborating International Partner Institutions:
 - Queen Mary's School of Medicine and Dentistry, London
 - University of New Mexico, Albuquerque, NM
 - Institute of Genome Sciences, University of Maryland, Baltimore, MD
 - Cancer Epidemiology Division, NIH/NCI, Bethesda, MD
 - Center for Genomics Research and Global Health, NIH/NHGRI, Bethesda, MD
 - Greenebaum Cancer Center, University of Maryland School of Medicine, MD
 - Institute of Human Virology, University of Maryland, Baltimore, MD



HPV Associated Cancers

291 million women worldwide (Point prevalence 10.1%) are estimated to have human papillomavirus infection of the cervix at a given point in time





HPV Carcinogenesis

- There are more than 100 types of HPV infecting humans
- Almost all African women are infected by hrHPV at some point in their lives
- Persistent hrHPV is a necessary but not sufficient cause of cervical cancer
 - HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-45, HPV-52, HPV-58, HPV-68 and HPV-69 are recognized as carcinogenic – 71% of global ICC are believed to be due to types 16 and 18
 - Recently classified as carcinogenic HPV-39, HPV-51, HPV-56, HPV-59
- Smoking, diet, sexual health and behavior are independent risk factors
- There is significant regional variation within Africa in cervical cancer incidence



Epidemiology of HPV Infection

- Persistent infection with hrHPV infection occurs in only 4 12%
- There is little data on prevalence of persistence and its determinants in African populations
- hrHPV infection leads to progressive changes in the cervical epithelium that can be detected before frank malignancy
- Estimated absolute risk for CIN3+
 - 47.4% (95% CI = 34.9% to 57.5%)
 - > 12 years of follow up after 2 positive qualitative type specific hrHPV
- Estimated absolute risk for CIN3+ or worse 3.0% (95% CI = 2.5% to 3.5%)
 - following a qualitative hrHPV test



Pattern of HPV infections in Nigerian women



- We studied 278 women enrolled in cervical cancer screening programs at 2 sites in Abuja, Nigeria
- Among HIV+ women, HPV35 (8.7%) and HPV56 (7.4%) were the most prevalent hrHPV types, while HPV52 and HPV68 (2.8%, each) were the most prevalent among HIV- women
- HIV infection was associated with increased risk of any HPV, hrHPV and multiple HPV infections.



High risk HPV in HIV+ and HIV- women

- The multivariate prevalence ratio for any hrHPV and multiple hrHPV were 4.18 (95% CI 2.05 – 8.49, p-value <0.0001) and 6.6 (95% CI 1.49 – 29.64, p-value 0.01) respectively, comparing HIV+ to HIV- women
- Oncogenic HPV types 35, 52, 56 and 68 may be more important risk factors for cervical pre-cancer and cancer among women in Africa. Current HPV vaccines do not cover the prevalent hrHPV types in this population and degree of cross reactivity of the vaccine needs to be ascertained.

Vaginal microbiome and prevalent high risk HPV infection in Nigerian women

In the same women, we characterized the vaginal bacterial composition and abundance (community state type, CST) by deep sequencing of barcoded 16S rRNA gene fragments (V4) and compared this by prevalent hrHPV status using logistic regression, weighted UniFrac distances, and LDA (Linear Discriminant Analysis) effect size (LEfSe) algorithm





Vaginal microbiome and prevalent high risk HPV (hrHPV) infection in Nigerian women

Our findings

- CST IVB, (Characterized by low relative abundance of Lactobacillus spp.) most prevalent CST present in 139 (50%)
- CST III (often dominated by *L. iners*) in 109 (39.2%)
- CST I (often dominated by *L. crispatus*) in 22 (7.9%)
- CST CST VI (dominated by *Proteobacteria*) in 8 (2.9%) participants previously undescribed.
- Association between CST IVB and hrHPV in HIV negative participants (adjusted OR = 5.63, 95%CI 1.19–26.7, p=0.03).
- LEfSeE analysis revealed an association between prevalent hrHPV infection and increased microbial diversity, with a decreased abundance of *L. iners* and increased abundance of anaerobes particularly of the genera *Bacteriodetes* and *Fusobacteria* in HIV- women.



Genomic risk of prevalent hrHPV infection in Nigerian women

- Sgnificant associations with 2 SNPs rs2305809 on Ribosomal Protein gene S19 (RPS19) and rs2342700 on Thymidylate Synthase gene (TYMS) and prevalent hrHPV infection.
- Genes/regions in the immune genes 2',5' oligoadenylate synthetase gene 3 (OAS3), sulfatase 1 (SULF1), epidermal dysplasia verruciformis (EV)associated EVER1 and EVER2 genes, transmembrane channel-like 6 and 8 (TMC6, TMC8), peroxiredoxin 3 (PRDX3), interleukin 2 receptorα (IL2RA), telomere maintenance 2 (TELO2), and complement component 1, r subcomponent-like (C1RL) were not associated.
- RPS19 gene codes for a ribosomal protein expressed by hematopoietic and non-hematopoietic tissues while TYMS gene product is used in the DNA synthesis and repair pathway.

Epigenetics of HPV infection







Epigenetics of HPV





Epigenetics of HPV 16 L1.3 and HPV 18 L2

HPV16 L1.3

HPV18 L2





Epigenetic changes in somatic cervical cells







Summary of results of Cervical somatic cells epigenetics





Reproducibility LMX1 -Corr.=0.525; Corr=0.694





Current ACCME research –

Epidemiology and carcinogenesis of hrHPV

- The pilot work done till date provides a foundation for the current research in ACCME
- Aims:

-Study the epidemiology and molecular genetic patterns of persistent hrHPV infection African women

- Prevalence of persistent hrHPV infection
- Multiple hrHPV infections
- Differential duration of persistence of specific hrHPV types in individuals with multiple hrHPV and their association with CIN2+
- Evaluate the epidemiological risk factors for persistent hrHPV infections

Gaps in knowledge about the role of the vaginal microenvironment

- Evaluate the epidemiological determinants and role of epigenetic changes in hrHPV and cervical cells as biomarkers of persistent hrHPV infection and CIN2+.
 - Determine the pattern of epigenetic changes in hrHPV and cervical cells, and its association with persistence of infection and CIN2+
 - Analyze the epidemiological determinants and secular trend of epigenetic changes in hrHPV and cervical cells in each category of hrHPV status and CIN2+
- Evaluate the role of cervical cytokines and that of the classes and stability of the vaginal microbiota and their association with persistent hrHPV infection and CIN2+
 - Examine germline risk factors for
 - persistent hrHPV infection
 - patterns of cervical cytokines secretions
 - pattern and stability of vaginal microbiome
 - CIN2+ in African women



Study procedures and participants' flow for ACCME projects Cases-pink; Controls-blue

Data Management Center



How old are you? : Refresh Plot

Total (N)	Missing	Unique	Min	Мах	Mean	StDev	Percentile						
							.05	.10	.25	.50 Median	.75	.90	.95
1009	<u>11 (1.1%)</u>	48	18.00	61.00	37.43	7.75	26.00	28.00	32.00	37.00	43.00	47.00	51.00

Lowest values: 18, 19, 19, 20, 20 Highest values: 59, 60, 60, 60, 61



Institute of Human Virology, Nigeria Institute of Human Virology, Nigeria

HPV and Cervical Cancer

Record Status Dashboard (all records)

Displaying record "through "N0050NHA"

Displayed below is a table listing all existing records/responses and their status for every data collection instrument (and if longitudinal, for every event). You may click any of the colored buttons in the table to open a new tab/window in your browser to view that record on that particular data collection instrument. Please note that if your form-level user privileges are restricted for certain data collection instruments, you will only be able to view those instruments, and if you belong to a Data Access Group, you will only be able to view records that belong to your group. Legend for status icons: Incomplete Unverified Complete

Study ID	HPV Infection in Nigerian Women 0- Baseline/Enrollment Visit	Physical Examination Form 0- Baseline/Enrollment Visit	Physical Examination Form 1- 6 months follow up	Physical Examination Form 2- 12 months follow up	Physical Examination Form 3- 18 months follow up	Physical Examination Form 4- 24 months follow up	Food Frequency Questionnaire 0- Baseline/Enrollment Visit	Food Frequency Questionnaire 1- 6 months follow up	Digital Cervicograph 0- Baseline/Enrollme Visit
	۲	۲	۲	۲	۲	۲	۲	۲	۲
N0001NHA	۲	۲	۲	۲	۲	۲	۲	۲	۲
N0001UATH	۲	۲	۲	۲	۲	۲	۲	۲	۲
N0002NHA	۲	۲	۲	۲	۲	۲	۲	۲	۲
N0002UATH	۲	۲	۲	۲	۲	۲	۲	۲	۲
N0003NHA	۲	۲	۲	۲	۲	۲	۲	۲	۲
N0003UATH	۲	۲	۲	۲	۲	۲	۲	۲	۲
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▼ of 1021 records



Laboratory resources





Laboratory resources









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- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health
- IHVN Research Department Staff and collaborators