

CHARACTERIZATION OF HPV-SPECIFIC T-CELLS IN BLOOD AND TISSUE IN UGANDAN WOMEN LIVING WITH HIV WITH CERVICAL LOW GRADE SQUAMOUS INTRAEPITHELIAL LESIONS

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Background Cervical cancer (CC) is the most common cancer in women living with HIV (WLWH) and the leading cause of cancer mortality in women in Uganda.^{1,2} CC occurs in a fraction of unresolved high-risk human papilloma virus (hrHPV) infections. HIV is a risk factor for hrHPV infection, however, infection and early stage, low grade squamous epithelial lesions (LSIL), can be resolved by a competent immune response. Nevertheless, WLWH with immune function restored by antiretroviral therapy (ART) remain at higher risk for persistent hrHPV infection, LSIL and progression to high grade squamous epithelial lesions (HSIL).³ Therefore, we hypothesize that the immune response differs between WLWH, on ART, who progress from LSIL to HSIL/ICC, compared to WLWH, on ART, who experience LSIL regression.

Methods Recently, a cohort (n=304) of Ugandan WLWH and HIV seronegative counterparts was established to categorize hrHPV status and examine associations with the immune response.⁴ When stratified by degree of dysplasia, hrHPV infection was more prevalent in WLWH with LSIL (cervical intraepithelial neoplasia (CIN) 0/1), compared to seronegative women, than the same comparison in HSIL (CIN2/3).⁴ Due to the scale of this study, immune parameters analyzed were limited to CD4 and CD8 counts and ratio. This prompted us to design a pilot study, subsampling the cohort, for in-depth interrogation of the immune response in LSIL. The study involves analysis of formalin fixed paraffin embedded (FFPE) cervical tissue and peripheral blood mononuclear cells (PBMC) from WLWH, on ART, diagnosed with LSIL associated with hrHPV infection with progression (n=4) or regression (n=4) or WLWH with no dysplasia diagnosis (n=4).

Results We developed a mass cytometry panel incorporating markers of T cell dysregulation and mucosal homing and leveraged combinatorial tetramer technology to analyze PBMC-derived T cell responses to antigens from various hrHPV types. Further functional analysis is being performed using cytokine intracellular staining (ICS) flow cytometry. FFPE-derived DNA and RNA are subject to TCR sequencing and immunology gene focused-Nanostring analysis, respectively, to complement peripheral immune response data. Owing to complexities of sample procurement, data analysis is ongoing.

Conclusions LSIL represents a reversible stage in the development of CC, with recent data³ suggesting this may be associated with poorer resolution of hrHPV infection in WLWH, compared to seronegative women. In this pilot study, we expect to identify features of immune dysregulation underlying increased risk of malignant progression from LSIL, which could propel larger scale high dimensional analysis of the cohort.

REFERENCES

1. C. de Martel, M. Plummer, J. Vignat, and S. Franceschi, Worldwide burden of cancer attributable to HPV by site, country and HPV type, *Int. J. Cancer*, **vol. 141**, no. 4, pp. 664–670, Aug. 2017, doi: 10.1002/ijc.30716.
2. F. Bray, J. Ferlay, I. Soerjomataram, R. L. Siegel, L. A. Torre, and A. Jemal, Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality

worldwide for 36 cancers in 185 countries, *CA. Cancer J. Clin.*, **vol. 68**, no. 6, pp. 394–424, 2018, doi: 10.3322/caac.21492.

3. S. Blitz *et al.*, Evaluation of HIV and highly active antiretroviral therapy on the natural history of human papillomavirus infection and cervical cytopathologic findings in HIV-positive and high-risk HIV-negative women, *J. Infect. Dis.*, **vol. 208**, no. 3, pp. 454–462, Aug. 2013, doi: 10.1093/infdis/jit181.
4. C. Nakisige *et al.*, Multiple High-Risk HPV Types Contribute to Cervical Dysplasia in Ugandan Women Living With HIV on Antiretroviral Therapy, *J. Acquir. Immune Defic. Syndr.* 1999, **vol. 90**, no. 3, pp. 333–342, Jul. 2022, doi: 10.1097/QAI.0000000000002941.

Ethics Approval This study including the informed consent process and consent forms in English and Luganda was approved by the Fred Hutchinson Cancer Research Center Institutional Review Office, the UCI Research Ethics Committee and the Uganda National Council for Science and Technology. All participants gave informed consent.

Consent De-identified patient information from this cohort was obtain through approval by the institutional review board at the Fred Hutchinson Cancer Center (IR File#: 10496)

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