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Impact of HIV on HPV-mediated cervical disease progression

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In the pre-antiretroviral therapy (ART) era, a 1987 U.K. case series suggested that young women living with HIV could have shockingly rapid progression of cervical dysplasia to carcinoma [1]. Data from 1988-1991 confirmed the likely generalizability of this clinical observation [2-7], leading the U.S. Centers for Disease Control and Prevention to add cervical cancer to the list of AIDS-defining clinical conditions in their 1993 revision of the AIDS Surveillance Case Definition [8]. Still, cancer epidemiologists expressed considerable doubt as to whether HIV would increase the population prevalence of human papillomavirus (HPV)-mediated cervical cancer [9]. This doubt was laid to rest with evidence of a surge in cervical cancer related to HIV infection, with even more dramatic causal inference for anal cancer [10,11]. It is plausible that given a comparatively long time from HPV infection to development of cervical cancer that women in the pre-ART era died of HIV disease before they could develop cervical cancer.

Fast forward 40 years and *AIDS* is publishing a systematic review and meta-analysis as to whether women living with HIV have higher risk of HPV infection, precancerous lesions, and cervical cancer [12]. This review is most helpful, as the relevant literature has grown; a February 2018 PubMed search of HIV in association with HPV, cervix, cervical or papillomavirus yields over 7000 articles. Justifying concerns expressed early in the epidemic, Liu *et al* document the substantial evidence that indicates the association of HIV with both a higher incidence of HPV and also a lower HPV clearance rate [12]. Women living with HIV who had lower CD4+ cell counts and/or higher HIV viral loads were more likely to acquire oncogenic HPV infection, and less likely to clear HPV, but these risk factors were mitigated, in part, when the women were on ART. Data were sufficient to conclude that incidence of low-grade squamous intraepithelial lesions (LSIL) was lower with ART use, but available data were more limited for whether ART lowered incidence of high-grade SIL (HSIL). Longer duration of ART use was associated with HSIL protection. LSIL regression was less likely among women living with HIV than among HIV-uninfected women, but was more likely among those women who were on ART and/or had higher CD4+ cell counts. Data were very limited in the study of HSIL regression, but no association with HIV-positive status was noted [12].

The systematic review and meta-analysis validates the many global efforts since the early 1990s to screen and treat women living with HIV for pre-cancerous cervical disease and/or HPV infection [13, 14]. In Africa, prevention and early diagnosis are crucial in the context of high burdens of both HIV and HPV, and limited cervical cancer treatment availability [15]. HPV vaccine is a tool that could eventually eliminate cervical cancer as a major preventable scourge of women worldwide [16]. Until then, screening tools such as visual inspection with acetic acid, cervical cytology, and/or cervicography, combined with therapies designed to ablate pre-cancerous lesions, can be effectively deployed in low-resource settings [17]. High-risk HPV DNA screening may also be a viable alternative in some settings [18]. Demonstrating the feasibility of widespread cervical cancer screening linked to HIV care in low- and middle-income countries was critical to motivating the Pink Ribbon Red Ribbon partnership to reduce deaths from cervical and breast cancer in low- and middle-income countries [19]. This effort is a remarkable advocacy, policy, and fund-raising effort that brings the influence and resources of The George W. Bush Institute, the President's Emergency Plan for AIDS Relief (PEPFAR), Susan G. Komen for the Cure®, UNAIDS, and at least 15 other major partners in industry, philanthropy, development, government, and advocacy spheres [19]. PEPFAR is poised to make additional investments in cervical cancer screening for women living with HIV in high-burden countries in 2018.

The world has learned much from its efforts to control the HIV epidemic. The cervical cancer prevention agenda nested within these global efforts is a paradigm for non-communicable diseases (NCDs) and HIV in the ART era [20-22]. As national governments, and programs like PEPFAR and the Global Fund to Fight AIDS, Tuberculosis and Malaria, succeed in placing millions of new persons each year on ART, the population of people who are living with HIV and are only partially immune-reconstituted is aging and at increasing risk of developing NCDs. At the same time, HIV has transitioned to a chronic disease whose health service delivery resembles that for NCDs. Ultimately, the substantial HIV and tuberculosis service delivery platforms established by Ministries of Health around the globe should be leveraged to screen for, diagnose and treat a host of other chronic diseases, including cancer, hypertension, heart disease, diabetes, mental health disorders, rheumatic diseases, and many others [23-27].

The efforts of GAVI's *The Vaccine Alliance* have supported the success of HPV vaccine demonstration projects and national HPV vaccine introductions in low- and middle-income countries, with a goal of vaccinating 20 million girls against HPV infection by 2020. Such prevention investments, combined with national programs for appropriate screening, early diagnosis and treatment of precancerous lesions, can help us achieve the elimination of cervical cancer as a major public health burden [28]. The inspiration of smallpox eradication and imminent eradication of polio and dracunculiasis suggests that it is possible with global partnerships like PEPFAR, Pink Ribbon Red Ribbon, and GAVI.

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