The synergistic health syndemic of HIV and cancer of the cervix in women living with HIV in sub-Saharan Africa: Decrying the dearth of information

The evolution of HIV treatment and care means that currently, people living with HIV (PLHIV) rarely die from the HIV infection course itself. The Joint United Nations Programme on HIV/AIDS (UNAIDS) reports that mortality in PLHIV is now due to the four main non-communicable diseases (NCDs) – diabetes, cancer of the cervix (CaCx), cardiovascular disease (CVD) and chronic respiratory illnesses.[1]

The dual burden of HIV infection and CaCx, an NCD, in sub-Saharan Africa (SSA) represents a complex public health challenge that demands concerted efforts and focused interventions. Antiretroviral therapy (ART) has extended the life expectancy of PLHIV, but it has also raised their risk of developing NCDs as they age.[2] Women living with HIV (WLHV) may be at increased risk of NCDs for various reasons, including the traditional NCD risk factors, direct consequences of HIV infection and exposure to specific antiretrovirals.[3] As such, the prevalence of NCDs is rising in many nations that have an HIV epidemic.[3] Therefore, highlighting the interplay between ART and the incidence of CaCx in WLHV can illuminate potential pathways for integrated disease management and prevention strategies, including patient education in the region.

SSA is home to two-thirds (67%) of PLHIV.[4] CaCx is the most common cancer in half (23/46) of the countries in SSA.[5] In 2020, an estimated 20% of all CaCx cases occurred in SSA.[6] The global age-standardised rate is 13.3 per 100 000 women-years, and yet, that of SSA ranges between 23.0 and 40.1 per 100 000 women-years.[6] Therefore, generating evidence that leads to the understanding of the impact of ART on the incidence of CaCx in WLHV should be a priority in SSA.

There is a six-fold increased risk of developing CaCx among WLHV.[7] Khalil *et al*.[8] showed that an estimated 20% of CaCx cases in SSA were attributable to HIV. However, the issue of whether ART is associated with a higher incidence of CaCx remains unresolved. Studies have shown that the incidence of human papillomavirus (HPV)-related malignancies such as CaCx has increased in the ART period,[9] while that of some of the most prevalent malignancies that define AIDS, such as Kaposi's sarcoma and non-Hodgkin lymphoma, has significantly decreased.[10] HPV and HIV type 1 (HIV-1) have both been identified as carcinogens by the International Agency for Research on Cancer.[11] HPV is a direct carcinogen, while HIV-1 is an indirect carcinogen owing to it causing immune suppression.[11] Recently, it has been hypothesised that HIV and its auxiliary proteins can directly promote carcinogenesis in a manner similar to mechanisms described for known oncogenic viruses.[12,13] According to Stier *et al*.,[14] in PLHIV, HPV-related malignancies continue even after apparent immune reconstitution following ART. Conversely, some studies have shown that the risk of acquiring CaCx is not increased in WLHV on ART.[15] Another study showed that it is immunodeficiency *per se* that results in certain cancers, including CaCx.[16]

However, according to the latest evidence, early ART commencement and continued adherence are likely to lower the frequency of precancerous cervical lesions, slow their progression and eventually lower the risk of CaCx.[17] In a systematic review and meta-analysis, Kelly *et al*.[17] showed that among 15 846 women living with HIV, ART was associated with a reduction in invasive CaCx incidence (crude hazard ratio 0.40, 95% confidence interval 0.18 - 0.87, I^2=33%). However, the CaCx rates in WLHV on ART show geographic variations. In a systematic review and meta-analysis by Rohner *et al*.,[18] when CaCx rates in women on ART for 5 years were compared with women in Europe, they were more than twice as high in Latin America and 11 times higher in South Africa (SA), but comparable in North America, suggesting that there are geographic influences.

WLHV are at increased risk of HPV acquisition, persistent HPV infection and faster progression to cervical dysplasia and cancer than women without HIV.[19] HPV is causally linked to CaCx, even though it is not a sufficient cause for CaCx. HIV has been established as a cofactor in the development of CaCx following HPV infection.[20] CaCx develops slowly; however, the natural history is accelerated in WLHV.[21]

With the advent of ART, WLHV have longevity of life. Immune abnormalities in PLHIV do not always reverse with ART.[22] It could be that prolonged survival in the background of ART use provides more time for the development of HPV-related cancers, as immune abnormalities persist.

However, CaCx is largely preventable by adopting primary (vaccination) and secondary prevention strategies.[10] Again, one of the reasons for not seeing declines in CaCx prevalence and incidence could be that the pre-existing HPV infections occur and progress before the commencement of ART for the treatment of HIV infection.[23] This is plausible, also taking into consideration the fact that the current cases are occurring in women who were not part of the HPV vaccination programmes, since the earliest programme in SSA was implemented in 2014 (in SA).[10] Therefore, any vaccination-related reduction in cancer is likely to manifest only several decades from now.[10]

However, there is a dearth of information on this topic. As recent as 2020, Lekoane *et al*.,[24] having conducted a scoping review on the subject in SSA, concluded that there persists a dearth of research on HPV-related malignancies among HIV-positive individuals in many SSA countries. Only a handful of studies, at the global level, have studied the impact of ART on CaCx in WLHV.[17,18] This is despite Denslow *et al*.,[25] as far back as 2014, commenting that 'an important gap in the literature is the effect of HAART (highly active antiretroviral therapy) use and progression of cervical lesions'. Large cohort studies would be required to evaluate the effects of ART on the incidence of CaCx, which might be a worthwhile investment if we are to understand this topic and make a dent in the incidence of CaCx in WLHV.

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