Response to Invited Commentary

Clifford et al. Respond to “Biological and Clinical Insights From Epidemiologic Research Into HIV, HPV, and Anal Cancer”

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We agree with Engels and Madeleine (1) that we may yet see declines in anal cancer incidence among human immunodeficiency virus (HIV)–infected persons in high-income countries as combined antiretroviral therapy (cART) is used increasingly earlier. This belief is based on the findings that immunodeficiency appears to particularly influence anal cancer risk years before cancer diagnosis, and that a large proportion of the excess anal cancer risk attributable to immunodeficiency can be explained by only moderately decreased CD4+ cell counts. The relationship between CD4+ cell counts and anal cancer risk in the Swiss HIV Cohort Study (Table 3 in our original article (2)) can provide a rough estimate of the fraction of anal cancer that is avoidable through different improvements in immunostatus. By applying the Bruzzi method (3), we estimate that avoiding having CD4+ cell counts drop below 200 cells/µL 6–7 years prior to anal cancer diagnosis would prevent 20% of anal cancer cases; this estimate rises to 49% or 79% by preventing CD4+ cell counts from dropping below 350 cells/µL or 500 cells/µL, respectively. Hence, even in high-income countries, cART may not have been initiated early enough to have prevented the establishment of a large proportion of irreversible precancerous anal lesions.

It is also worthwhile to consider the extent to which the epidemiology of anal cancer may be extrapolated to predict the impact of cART on cervical cancer, which is still the most important cancer in women in many of the lowest-income countries (4). Paradoxically, the effects of HIV-related immunodeficiency and cART on cervical cancer have been more difficult to establish than their effects on anal cancer for 2 main reasons. First, cervical cancer has been classified since 1993 as an acquired immunodeficiency syndrome (AIDS)–defining cancer, which created problems for the early studies of women with AIDS that were based on linkages with cancer registries, because incidence rate analyses had to exclude many prevalent cervical cancers coinciding with AIDS onset. These studies failed to identify significant associations between CD4+ cell counts at AIDS onset and the risk for either in situ or invasive AIDS onset and the risk for either in situ or invasive cervical carcinomas (5). Nevertheless, cohort studies of HIV-infected women in high-resource countries are now revealing that cervical cancer incidence is clearly related to CD4+ cell counts (6) in a linear way that resembles the relationship with anal cancer (2) rather than the much steeper one found for Kaposi sarcoma or non-Hodgkin lymphoma. Findings on cervical cancer extend, therefore, the previous knowledge that low CD4+ cell counts increase cervical human papillomavirus persistence (7) and the incidence of cervical squamous intraepithelial lesions (8). Second, cervical cancer is preventable through screening, so the intense surveillance and treatment of precursor cervical lesions in well-studied cohorts of HIV-infected persons in high-income countries have substantially curbed the cervical cancer burden (9).

The large majority of HIV-infected women in the world live in sub-Saharan Africa, where cervical cancer incidence rates in the general population are up to 10 times higher than in the United States (4). Access to cART is now increasing in sub-Saharan Africa and other low- and middle-income settings far more rapidly (10) than is access to high-quality cervical screening. Prolonged survival because of cART use will probably lead to a similar increase in cervical cancer incidence in HIV-infected women, as has been seen for anal cancer incidence in high-income countries in the first years after cART introduction (9, 11, 12). If, as for anal cancer, a large proportion of the excess cervical cancer risk attributable to HIV-related immunodeficiency can also be explained by only moderately decreased CD4+ cell counts, then the earliness at which HIV infection is detected and cART is subsequently initiated will be, in combination with human papillomavirus vaccination and cervical screening, key to the prevention of cervical cancer in HIV-positive women in low-income countries.
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REFERENCES