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CORRESPONDENCE

Reply to P. De Paoli et al

We are grateful for the correspondence provided by De Paoli and Carbone[1] regarding our recently published Comments and Controversies piece focused on HIV-associated cancers. Their letter provides an important extension of some of the main points articulated in our article. Indeed, we wish to acknowledge our correspondents' own excellent review also highlighting the complexity and heterogeneity of cancers occurring in the HIV-infected population.[2]

In our article, we had suggested that epidemiologic groupings (AIDS-defining *v* non–AIDS-defining cancer; infection related *v* infection unrelated) may be only partially informative if these are not clearly informed by underlying biologic mechanisms. In their letter, De Paoli and Carbone[1] have extended this view by highlighting a need for strict criteria establishing pathogenetic associations between infectious agents and cancer, suggesting for example caution when viruses are implicated in carcinogenesis based on polymerase chain reaction (PCR) detection, without accompanying demonstration that the virus infects tumor cells using other techniques.

We wholeheartedly agree, and their comments are particularly important given that cancers caused by oncogenic viruses continue to exact an enormous toll among people living with HIV globally. One relevant example may be head and neck squamous cell carcinoma (HNSCC). As described in our article, HNSCC incidence is increased among HIV-infected individuals compared with those without HIV, although whether this represents increased rates of tobacco and alcohol use, increased prevalence of oral oncogenic human papillomavirus (HPV) infection, immunosuppression, or some combination has remained largely unclear. Notably, a recent study suggested largely similar risk factor associations for HNSCC in HIV-infected and -uninfected people, using a composite method to define HPV positivity in HNSCC tumors based on PCR, in situ hybridization, and p16 immunohistochemistry (IHC).[3] Importantly, discordant results between p16 IHC and HPV PCR are relatively common, and the clinical and biologic significance of such discrepancies remains uncertain.[4] Other studies using a single method may therefore misclassify cases as HPV positive versus HPV negative, leading to erroneous conclusions.

For all these reasons, efforts to standardize criteria for defining pathogenetic associations between infectious agents and cancer are certainly needed. Along with molecular insights, we also agree that additional research, such as the careful study of drug-drug interactions, is needed to improve the treatment of HIV-infected patients with cancer. We therefore appreciate the comments of De Paoli and Carbone[1] in this regard.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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