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HAART and lungs: Do HIV protease inhibitors impact cancer risk?

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Highly active combination antiretroviral therapy (HAART) dramatically altered the natural history of HIV infection and its complications, including that of cancers in the setting of HIV. HAART is associated with a 50-80% absolute decrease in incidence of Kaposi sarcoma (KS) and certain AIDS-defining non-Hodgkin lymphomas that occur in patients with low CD4+ counts. While these cancers remain the commonest tumors in people with HIV and a substantial global health problem - especially in parts of Africa, other cancers are an increasingly important public health concern. HIV increases the risk of smoking related tumors such as lung cancer; high-risk human papilloma virus (HPV)-associated tumors such as cervical cancer, anal cancer, and oropharyngeal cancers; Hodgkin lymphoma; and several other malignancies. Indeed, the burden of most tumors other than KS and non-Hodgkin lymphoma continue to increase over time in HIV-infected populations in part due to substantially improved longevity and aging[1]. An important HIV-associated cancer in the HAART era is lung cancer. In 2010, there were an 840 cases of lung cancer among 900,000 people with known HIV in the US alone, making it the third commonest cancer in this patient population[2]. While lung cancer risk is partially attributable to a high smoking prevalence in some HIV-infected populations, HIV remains an independent risk factor[3]. The pathogenic mechanisms for this observation are incompletely understood, and an effect of HAART on lung cancer risk in people with HIV has not been firmly established.

In this issue of *AIDS*, Bruyand *et al.* ask a provocative question about the potential effect of HIV-protease inhibitors (PIs) on modulating risk of lung cancer. First generation PIs were approved by the U.S. Food and Drug Administration in 1996 and remain a common backbone to many HAART regimens. The hypothesized specific effects of PIs on lung cancer risk are two-fold. First, this class of drug is notable for inhibition of p450 cytochrome enzymes, which alters the metabolism of many drugs. Indeed strong CYP3A4 inhibition by ritonavir has been exploited to boost levels of other antiretroviral agents and allow for once-a-day regimens. However, the cytochrome p450 system also plays a role in the activation and metabolism of tobacco smoke derived carcinogens such as polyaromatic hydrocarbons and nitrosamines[4]. Several polymorphisms in specific p450 have been associated with lung cancer; however the effect of strong inhibitors of the p450 system on metabolism of tobacco smoke containing carcinogens and subsequent lung cancer risk are unknown.

Secondly, although this class of drugs targets HIV aspartate proteases involved in virion polyprotein processing, they do have some off-target effects on signaling pathways that may be important in lung carcinogenesis. The best studied of these is the effect of nelfinivir on akt signaling[5]. As a downstream mediator of phosphatidylinositol 3'-kinase (PI3K), akt is increasingly activated in bronchial epithelium in specimens ranging from normal, through reactive changes and bronchial dysplasia, to lung cancer, and akt has been considered a target of interest for lung cancer prevention studies[6]. Several oncology studies have evaluated nelfinivir as an anti-neoplastic agent and akt inhibition can be demonstrated *in vivo* in peripheral blood mononuclear cells[7].

Bruyand and colleagues evaluated their PI hypothesis in a nested case-control study of smokers or ex-smokers with living with HIV across three large French hospital-based cohorts. 383 lung cancer cases diagnosed 2000-2011 and 1064 age and sex matched controls were included in the study. HAART prescribing information and CD4+ data were available for cases and controls. Analyses were adjusted for smoking status (current versus ex-smokers) and nadir CD4+ count. Greater than 90% of cases and controls had been prescribed HAART, and ~80% had a history of PI exposure. Control of HIV viremia at time of diagnosis was comparable between cases (71%) and controls (78%). Given strong p450 inhibition, ritonavir use was evaluated separately in a sensitivity analysis. Importantly, the authors found that exposure to PIs did not increase cancer risk (odds ratio 0.83, 95% confidence interval 0.61 – 1.12). Results were similar when analysis was limited to ritonavir alone or to current smokers. One of the strengths of the study was the large number of cases included and information on HIV and smoking related variables in these well-characterized French cohorts.

While the results of the primary hypothesis about PI risk on cancer were null, it would be premature to conclude that PIs have no effect on risk of lung cancer or other cancers. The primary findings may in part be due to the definition of PI exposure. Interestingly, analysis limited to PI exposures initiated 5 years before the index date suggested a decreased cancer risk. Several recent epidemiologic studies of HIV-associated Hodgkin lymphoma and anal cancer have demonstrated that decreased risk may be noted only after 5 years or more of HAART[8, 9]. Furthermore, cumulative HIV viremia is emerging as a better marker of cancer risk than evaluation of single time points, and before concluding that PI-based regimens were specifically associated with decreased risk, an evaluation of cumulative HIV viremia would be required. Nonetheless, given the biologic plausibility of decreased lung cancer risk due to off-target akt inhibition and/or decreased activation of tobacco smoke containing carcinogens by p450 cytochromes, the findings by Bruyand and colleagues are intriguing. It should be noted that a protective effect of PI-based HAART against AIDS-associated KS has also been explored. Although results have been conflicting, perhaps due to confounding factors such as KS-immune reconstitution syndromes and inadequate evaluation of time of exposure to PIs, a recent large Veteran's Affairs study found that after correcting for CD4 counts and HIV viral load, time on boosted (ritonavir-containing) PI-based HAART was associated with a decreased risk of KS[10] noted only after 3 years on therapy. If indeed PI-based therapy has a preventative effect against KS and perhaps lung cancer, this could have an impact on guidelines for "what to start" in certain HIV-infected

populations. Given the potential global health impact of cancer prevention for the ~35 million HIV-infected people worldwide, further evaluation of this important possibility is warranted.

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