

# HIV protease inhibitors to prevent progression of cervical intraepithelial neoplasia to cervical cancer: therapeutic opportunities and challenges

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Human papillomavirus (HPV)-related cancers remain one of the most common causes of cancer-related mortality worldwide [1]. HIV-infected women are at even higher risk of cervical cancers compared with HIV-uninfected women, and HIV-infected men and women are at increased risk of anal cancer compared with their HIV-uninfected counterparts [2–4]. HPV-associated cancers are largely preventable. Primary prevention is available through HPV vaccination to prevent cancers associated with vaccine HPV types (HPV 16 and HPV 18) [5,6]. Secondary prevention is accomplished through detection of high-grade cancer precursors such as cervical intraepithelial neoplasia (CIN) or anal intraepithelial neoplasia (AIN) and physical removal/destruction of these lesions to prevent progression to cancer. These measures are effective for preventing cervical cancer and their efficacy is inferred, although not yet definitively established for anal cancer. Treatment of high-grade precancerous lesions is invasive and associated with side-effects such as pain, bleeding, scarring and, in the case of CIN treatment, premature delivery [7]. Better strategies for eradication of precancerous lesions are clearly needed. The article by Barilleri *et al.* [8] points to a new approach to treat HPV-associated precancerous lesions, employing protease inhibitors commonly used to treat HIV infection to inhibit matrix metalloproteinases (MMPs).

There is a substantial body of evidence suggesting that expression of MMPs by cervical epithelial cells plays an important role in progression from CIN 3 to invasive cancer and, possibly, in spread of cancer once it has

developed [9,10]. Barilleri *et al.* demonstrate elegantly *in vitro* that cells derived from low-grade CIN express MMPs and that inhibition of MMP expression in these cells by HIV protease inhibitors saquinovir and ritonavir reduces their ability to invade in an *in-vitro* model.

What are the clinical implications of their findings? On the basis of their results, the authors propose that protease inhibitors may be useful to prevent progression of CIN 3 to cervical cancer. However, evidence of the efficacy of protease inhibitors to prevent cancer in clinical studies is limited at best. Although the authors cite studies demonstrating that HAART reduces the risk of cervical cancer in HIV-infected women, the data are not conclusive. Cancer registry and other studies have not shown a reduction in cervical cancer since the introduction of HAART [4,9]. Data on the effect of HAART on anal cancer and its precursors have shown that the incidence of anal cancer has actually increased, not decreased. Most studies have shown that HAART use is associated with limited or no reduction in the incidence of high-grade CIN or AIN [10–12]. Similarly, most studies have not shown any protective effect of HAART on cervical or anal HPV infection [10,13]. It must also be noted that none of the clinical studies cited by the authors showed that protease inhibitors prevent progression to cancer, an issue that can only be addressed in a randomized clinical trial, which cannot be done for ethical reasons.

Does this mean that saquinovir or ritonavir does not work as proposed by the authors? No. Studies of HIV-infected

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individuals on HAART have multiple limitations to address this question rigorously. Individuals in these studies were on a wide variety of HAART regimens, some of whom were not on protease inhibitors at all, and some of whom were taking different protease inhibitor regimens. As shown by the authors, different protease inhibitors have different effects on MMPs and, thus, different HAART regimens will vary with respect to their ability to inhibit MMPs, however, at this point, there is no evidence to recommend that treatment decisions for HIV infection, including choice of protease inhibitors, should be based on their purported effect on HPV-related lesions.

The authors rightly propose the use of protease inhibitors in HIV-uninfected individuals. As their results suggest that MMP inhibition may not inhibit cancers once they develop, they instead propose that protease inhibitors be used to treat CIN to prevent progression to cancer. However, as their results also show that at the concentrations used there was no induction of cell death or apoptosis of cells derived from a CIN lesion, CIN lesions may persist when patients are treated at doses leading to relatively low local tissue concentrations. Even if they reduce the risk of progression to cancer at these concentrations, a woman may need to take the protease inhibitor for as long as the lesion persists. As systemic use of protease inhibitors has side-effects, an interesting alternative approach would be to apply protease inhibitors topically. Higher local concentrations could induce apoptosis and, if so, this approach might lead to regression of high-grade CIN. Studies to address the local effects of topical protease inhibitors could be done for a limited period, with lesion regression as an endpoint and with close follow-up to ensure that patients have not progressed to cancer during the study.

Overall, Barilleri *et al.* are to be commended for pointing to a potentially interesting new approach for preventing HPV-associated cancers, particularly since the proposed drugs are already in use and associated with a well known toxicity profile. Their data highlight as many challenges as opportunities, but careful selection of the appropriate therapeutic target, such as high-grade cancer precursors and the appropriate approach to dosing, such as topical therapy, might lead to promising results that will benefit both men and women at risk of HPV-associated cancers.

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### Conflicts of interest

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