Cervical Cancer Screening of Women Living with HIV Infection: A Must in the Era of Antiretroviral Therapy

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Women living with human immunodeficiency virus (HIV) infection have a much higher risk of human papillomavirus infection and cervical cancer than do HIV-uninfected women. Before the introduction of antiretroviral therapy, the lack of cervical cancer screening among HIV-infected women probably had little influence on their life expectancies because of the high competing mortality associated with other causes, but the situation is changing rapidly everywhere. In sub-Saharan Africa, for instance, ~400,000 HIV-infected women were receiving antiretroviral therapy in 2005. Funds given to antiretroviral therapy programs in low-resource countries not only support the purchase of drugs, but they also support the development of clinical infrastructures and laboratories. Because women who receive antiretroviral therapy are observed regularly, they can also receive the continuity of care needed for cervical screening. Therefore, the real opportunity to prevent cervical cancer in HIV-infected women in low-resource countries should not be missed, especially as new, inexpensive screening methods (e.g., rapid human papillomavirus tests) are under evaluation.

At ~17.3 million, women make up almost one-half of the total number of persons living with HIV infection worldwide. A total of 13.2 million of these women live in sub-Saharan Africa [1]. Low- and middle-resource countries, where women have been hit hardest by the AIDS epidemic, have historically also had a very high prevalence of human papillomavirus (HPV) infection [2] and a high incidence of cervical cancer [3]. In the year 2000, sub-Saharan Africa experienced an estimated 57,000 cases of cervical cancer (i.e., 22% of cases of cancer among women) and an age-standardized incidence of 31 cases per 100,000 women [3]. By the age of 64 years, the cumulative risk of developing cervical cancer in Kyadondo, Uganda, was 3.26%, which is several-fold greater than the cumulative risk in England (0.62%) or among black women in the United States (0.75%). Furthermore, the cervical cancer incidence has not decreased in any region of sub-Saharan Africa in recent decades; in fact, significant upward trends have been reported in several areas [3, 4].

Because both HIV infection and HPV infection are sexually transmitted, the 2 infections are often found together [5, 6]. In addition, as a result of HIV-induced immune impairment, there is also an increased probability that HPV infection will become persistent in HIV-infected women [5] and evolve into precancerous and cancerous lesions of the cervix uteri [7–9]. As expected, the relative risk of invasive cervical cancer among women living with HIV infection varies from country to country on the basis of the extent to which premature death due to other causes or early detection of cancer [7] prevents progression of preinvasive lesions to the invasive stage.

Effective screening and early treatment of precancerous cervical lesions are, thus, key factors in preventing cervical cancer in both HIV-infected and HIV-uninfected women [10]. High-resource countries have been able to prevent cervical cancer among women with HIV/AIDS to different extents. In the United States, for example, a high percentage of women who receive treatment for HIV undergo annual Papanicolaou smears (81% [11]), and the vast majority (94%) of cases of cervical carcinoma among these women are detected at the in situ stage [7]. Screening also seems to have been successful in Scotland [12], although less so in southern Europe, where AIDS rates have historically been the highest in the continent [13, 14]. Strong (albeit indirect) evidence of under-use of cervical cancer screening in southern Europe includes the relatively high proportion of HIV-infected women for whom invasive cervical cancer is the AIDS-defining illness (e.g., 6.8% of patients in Spain [15]), as well as a lower percentage of carcinomas in the in situ stage (61.5%) among HIV-infected...
women in Spain [16] than in the United States [7]. In Italy, among 132 women identified during the period 1996–2004 with invasive cervical cancer as an AIDS-defining illness, one-half had their first positive HIV test result \( \geq 10 \) years before cancer was diagnosed [14]. This long interval suggests a failure to stop the progression of cervical precancerous lesions by means of adequate screening despite the knowledge of HIV infection.

The reasons for inadequate screening coverage of women living with HIV in southern Europe, despite ubiquitous access to antiretroviral therapy—and, thus, regular contact with medical services—are not clear. According to a survey of referral clinics for people with HIV infection in Italy [17], it seems that specialists are aware of the current guidelines on cervical cancer screening for HIV-infected women, but that the obstacles encountered are of an organizational nature (i.e., difficulties in combining routine follow-up of markers for HIV infection with gynecological examination, which is generally performed elsewhere) [17].

In contrast to high-resource countries, middle- and low-resource countries provide little or no access to cervical cancer screening for women, regardless of whether they have HIV infection [10]. Before the introduction of antiretroviral therapy, the lack of cervical cancer screening for HIV-infected women probably had little influence on their life expectancies because of high competing mortality associated with other causes, such as tuberculosis and opportunistic infections, but the picture is now rapidly changing. According to the Joint United Nations Programme on HIV/AIDS, access to antiretroviral therapy in low- and middle-resource countries increased from 240,000 persons in 2000 to 2.0 million persons in 2006 (i.e., there is access for 28% of those in need). In sub-Saharan Africa, \( \sim 1.3 \) million people were receiving antiretroviral therapy in 2006 (i.e., 28% of those in need) [18].

The incidence of Kaposi sarcoma, which was formerly the most important HIV-related malignancy, has decreased dramatically in high-resource countries in the antiretroviral therapy era [19, 20]. Therefore, the spread of antiretroviral therapy has the potential to reduce the enormous—and, thus far, increasing—burden of Kaposi sarcoma in sub-Saharan Africa (in many areas, it is the most common form of cancer in men and one of the most common forms in women) [3]. In contrast, the impact of the partial immune restoration induced by antiretroviral therapy on the natural history of HPV infection seems modest, at best [21], and the incidence of cervical cancer among women with AIDS has not decreased in high-resource countries since the introduction of antiretroviral therapy [19, 20]. Thus, HIV-infected women remain at a continued substantial risk for cervical cancer, even if they receive antiretroviral therapy. Other prevention strategies are urgently needed.

Cervical cancer screening programs in low-resource countries are difficult to implement and maintain for a variety of reasons, including cost, lack of trained personnel, inadequate laboratory support, and low patient follow-up rates. However, the scale-up of antiretroviral therapy in low-resource countries provides an unprecedented opportunity to develop cervical cancer screening programs. For example, in 2003, the United States announced the President’s Emergency Plan for AIDS Relief, which committed \$15 billion to HIV prevention and care programs in 15 low-resource countries [22]. These funds are used not only to purchase antiretroviral therapy, but also to provide training, development of treatment infrastructure, and laboratory support. Because women receiving antiretroviral therapy are observed on a regular basis, they can also receive the continuity of care needed for cervical cancer screening.

Of interest, to scale-up access to antiretroviral therapy in low-resource countries, the World Health Organization has proposed a shift from an individual-based approach to a population-based approach [23]. This approach implies standardized simplified treatment protocols and decentralized, integrated delivery of care.

The optimum methods for cervical cancer screening in low-resource countries remain to be determined. Cytological screening programs have curbed the cervical cancer incidence and mortality in high-resource countries, but elsewhere, even where cytological screening is widespread (i.e., in Latin American countries), high standards are difficult to implement [10]. Cytology samples may be poorly collected, and cytology laboratories may have deficient infrastructures, inadequate training and supervision, and lack of follow-up procedure for abnormal findings [10]. Visual inspection after application of acetic acid or Lugol’s iodine offers a low-cost alternative and has the advantage of immediate results, and, if necessary, treatment during the same visit. The validity of the test, however, is highly dependent on the training and skills of those performing it, and in some low-resource settings, the sensitivity to detect high-grade cervical lesions was reportedly \(< 50\% \) [24].

Screening for high-risk HPV types would have several advantages over other types of screening: it is more sensitive for high-grade cervical lesions and much less dependent on the quality of the sample and on human judgement than are cytologic and visual inspection [10]. The currently available HPV tests are too expensive for low-resource countries, but a cheaper reconfiguration of Hybrid Capture 2 (Digene) is in the pipeline [25]. The new assay includes 17 carcinogenic types, is relatively uncomplicated, and can produce \( > 100 \) results in a few hours, facilitating same-day follow-up examination and treatment, if necessary. For routine use, the new test will be fully automated.
The ultrasensitive detection of HPV is undesirable for clinical use, because it would produce unacceptably high levels of positive results among women who have low-viral load infections and may not require treatment. This problem is especially important among HIV-infected women, in whom a prevalence of carcinogenic HPV types of up to 85% has been reported [6, 26]. Thus, the cutoff sensitivity for HPV detection in the new assay has been adjusted to optimal clinical threshold. Conversely, additional sensitivity for detection of cervical intraepithelial neoplasia grade 3 and occult invasive cervical cancer has been gained by combining the E region (i.e., viral oncogenes) to L region for each HPV type [25].

In respect to cost-effectiveness, evaluation of the costs and clinical benefits of cervical cancer screening for HIV-infected women in low- and medium-resource countries is not available, but a study from the United States [27] revealed that annual Papanicolaou smears were associated with projected life expectancy benefits equal to or greater than those provided by other preventive measures in general medicine or HIV disease.

Great hope is currently vested in future universal HPV vaccination strategies, but for the moment, the efficacy of vaccination has been demonstrated only in healthy women who were not already infected with the HPV types included in the vaccine [28]. Clinical studies of the safety and effectiveness of the HPV vaccine that involve HIV-infected women are not yet available [29]. Of equal importance to the possibility of administering the HPV vaccine to HIV-infected women is finding out whether immunization prevents reinfection in women who have already been exposed to the HPV types present in the vaccine [28].

Thus, for the moment, the prevention of avoidable deaths due to cervical cancer rests only on early diagnosis. The real opportunity to prevent cervical cancer in women living with HIV infection in low-resource countries should not be missed.

Successful implementation of such screening programs will also teach valuable lessons that, we hope, can then be applied to all women, and not only to those with HIV infection.

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References

